Efficacy of Treating Chronic Hepatitis C Genotype 3 Infection with Peginterferon Alfa plus Ribavirin in Real-world Practice

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Background: *Chronic hepatitis C genotype 3 is a major public health problem worldwide. Standard treatment with peginterferon alfa plus ribavirin for 24 weeks is a recommended treatment in settings in which direct-acting antiviral agents are not available.*

Objective: *To evaluate the treatment efficacy in Thailand of peginterferon alfa combined with a ribavirin treatment regimen, and to evaluate parameters predicting treatment response.*

Material and Method: *Data were retrospectively retrieved of consecutive chronic hepatitis C genotype 3 patients who were treated with peginterferon alfa plus ribavirin for 24 weeks at Rajavithi Hospital, Bangkok, between 1st January 2013 and 31st December 2016. Clinical characteristics, compliance with treatment and laboratory data were reviewed. Sustained virological response (SVR) and predictors of treatment response were analyzed.*

Results: *A total of 119 patients completed treatment. Most were aged 40 years or more, and males accounted for 66.4%. Fifty-four percent of patients had BMI of more than 23 kg/m^2, and half of them had cirrhosis, which was defined as liver stiffness equal to or more than 12.5 kPa, and 97% of these had Child Class A while the remaining 3% had Child Class B. Baseline HCV RNA was less than 400,000 IU/mL in 42.9% of cases and equal to or more than 400,000 IU/mL in the other 57.1%. Overall 69.7% of patients achieved SVR, while 30.3% were non-responsive. Multivariate analysis revealed that liver stiffness of less than 12.5 kPa and compliance with the 80/80/80 adherence rule were associated with SVR with odds ratios of 6.50 (2.24 to 18.83) and 4.76 (1.64 to 13.82), respectively.*

Conclusion: *The efficacy of a standard treatment with peginterferon alfa plus ribavirin for chronic hepatitis C genotype 3 patients is satisfactory in real-world practice. Sustained virological response can be improved by selecting patients who are non-cirrhotic for treatment with this regimen and making them aware of the importance of complying with the 80/80/80 adherence rule.*

Keywords: *Chronic hepatitis C, Genotype 3, Treatment, Peginterferon alfa, Ribavirin, Sustained virological response*

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Hepatitis C virus (HCV) infection usually leads to chronic infection[1,2], which often follows a progressive course of fibrotic change in the liver, ultimately resulting in cirrhosis[3,4] and, therefore, increased risk of hepatocellular carcinoma at 1.4 to 2% per year[5,6]. The number of people worldwide infected with HCV is estimated at 180 million individuals, or 3% of the world's population, and the incidence of HCV infection is 1 to 2%[7] in Thailand, where HCV subtype 3a is the most predominant (36.4%), followed by subtypes 6 (20.9%), 1a (19.9%), 1b (12.6%), 3b (9.7%) and 2a (0.5%)[8]. Compared with other genotypes, genotype 3 is associated with hepatic steatosis and a more rapid progression of hepatic fibrosis[9].

The goal of treatment of HCV is eradication of HCV RNA, and this is predicted by an achievement of a sustained virological response (SVR) as defined by the absence of HCV RNA by polymerase chain reaction six months after cessation of treatment. SVR is associated with a 99% chance of having undetectable serum HCV RNA throughout a 4-year follow-up period[10] and leads to a marked reduction in the number of deaths, liver transplants, and liver-related morbidities and mortalities[11]. Meta-analysis of eight trials that included 1,225 genotype 3 patients revealed that peginterferon alfa combined with ribavirin 24 weeks

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treatment achieved overall SVR of 68%, with a range of 60% to 80%[12]. Because of the modest efficacy and frequent adverse side effects of interferon-based regimens, recent treatment guidelines for HCV have shifted to direct-acting antiviral agents (DAAs), which yield significantly higher SVR (98% to 99%) and fewer side effects[13,14]. Though DAAs are effective for patients with genotype 3 infection, access is restricted to some patients in many countries[15] including Thailand, where HCV genotype 3 has a high prevalence[8,16], but DAAs are not accessible to most patients. For this reason, the European and Asian-Pacific guidelines continue to recommend dual therapy with peginterferon alfa plus ribavirin in settings in which DAAs are not available[14,17].

There have been few studies on the effectiveness of this treatment regimen in Thailand; therefore, the present study aimed to evaluate treatment efficacy of peginterferon alfa combined with ribavirin for 24 weeks in HCV genotype 3 patients at Rajavithi Hospital, Bangkok, Thailand. The results should show the efficacy of this treatment regimen in real-world practice and may help public health policy-makers in Thailand to decide whether to continue recommending this treatment or change to the new direct-acting antiviral agents in the future.

Material and Method

A retrospective cohort study was conducted by reviewing the medical records of all chronic HCV genotype 3 patients who were treated with peginterferon alfa combined with ribavirin for 24 weeks at the out-patient clinic, Department of Medicine, Rajavithi Hospital between 1st January 2013 and 31st December 2016. The protocol of this research was reviewed and approved by the ethics committee of Rajavithi Hospital (No. 095/2560).

The inclusion criteria were as follows: persistence of anti-HCV antibodies and serum HCV RNA over at least 6 months; HCV genotype 3; aged 18-65 years; treatment naive; no history of alcohol abuse (or having abstained from alcohol for at least 6 months); presence of significant hepatic fibrosis determined by transient elastography (liver stiffness measurement equal to or more than 7.5 kPa)[18]; or histopathological staging equal to or more than F2 stage evaluated using the METAVIR scoring system. Exclusion criteria were the following: no decompensated cirrhosis; allergy to interferon/ribavirin; co-infections with hepatitis B or the human immunodeficiency virus (HIV); autoimmune disease; major depression; thyroid dysfunction; or other severe comorbid diseases.

Laboratory data were retrieved from medical records of patients at baseline, end of treatment and follow-up 6 months post treatment, including hematology, biochemistry, HCV RNA viral load and liver stiffness. The patients' clinical characteristics and compliance with treatment were evaluated, and those who were lost to follow-up or had incomplete medical data were excluded from the study.

Treatment protocol: patients were assigned to receive anti-HCV therapy with peginterferon alfa-2a dose 180 mcg or peginterferon alfa-2b dose 1.5 mcg/kg body weight subcutaneous injection weekly plus ribavirin dose 800 mg daily given orally in divided doses (typically 400 mg twice daily) or a weight-based ribavirin dose of 15 mg/kg for 24 weeks. Compliance with treatment in accordance with the 80/80/80 adherence rule, which was defined as taking at least 80% of each drug for at least 80% of the treatment duration, was recorded.

Serum HCV RNA (a real-time PCR-based assay with a lower limit of detection of less than 15 IU/ml) was collected at baseline, end of treatment and 6 months after cessation of treatment. The patients were classified into two groups according to response:

Sustained virological response (SVR): patients who had undetectable serum HCV RNA at the end of treatment and 6 months after cessation of treatment.

Non-response: those who detectable levels of serum HCV RNA at the end of treatment, or had a relapse of serum HCV RNA 6 months after cessation of treatment.

The potential baseline variables as treatment response factors included: sex, age, BMI, liver stiffness, baseline HCV RNA, type of peginterferon alfa and compliance with the 80/80/80 adherence rule, and these were analyzed.

Statistical analysis

Data analysis was performed using SPSS software version 17.0 (SPSS Inc., Chicago, Illinois, USA). Continuous data of baseline characteristics were presented as mean $\pm$ SD, median (range) and categorical data were shown as number (percentage). Continuous variables were compared using t-test or the Mann-Whitney U test while categorical variables were compared using the Chi-square test or Fisher exact test. Multivariate Cox regression analysis was used to determine the baseline variables predictive of response to treatment. Results were described as odds ratios with 95% confidence intervals, and a *p*-value of less

than 0.05 was considered statistically significant.

Results

A total of 119 patients completed treatment in accordance with the study protocol. Demographic and clinical characteristics of the patients are summarized in Table 1. Seventy-nine (66.4%) were male and 40 (33.6%) were female. Most patients (84%) were at least 40 years old, and 54.6% had BMI of more than 23 kg/m^2.

With regard to underlying liver fibrosis, 55.5% of patients had cirrhosis, defined as liver stiffness equal to or greater than 12.5 kPa[18], and 97% were classified into Child Class A while the remaining 3% were Child Class B. Baseline HCV RNA was less than 400,000 IU/mL in 42.9% of patients and equal or more than 400,000 IU/mL in the other 57.1%. Most patients (74.8%) complied with the 80/80/80 adherence rule. Overall 69.7% of patients achieved SVR and 30.3% were non-responsive.

Laboratory data presented in Table 2 show that all patients had good kidney function with estimated glomerular filtration rate of more than 60 ml/min/1.73 m^2, and most had satisfactory baseline hematologic findings and liver function test. Comparison between the two groups of patients (SVR and non-response) found that SVR was associated with liver stiffness, baseline HCV RNA, and compliance with the 80/80/80 adherence rule (Table 3).

Univariate analysis (Table 4) showed that liver stiffness of less than 12.5 kPa, HCV RNA less than 400,000 IU/mL, and compliance with the 80/80/80 adherence rule were associated with SVR with crude OR of 6.53 (2.46 to 17.36), 2.54 (1.09 to 5.92) and 3.94 (1.65 to 9.44), respectively; however, multivariate analysis revealed that just liver stiffness of less than

Table 1. Demographic and clinical characteristics of chronic hepatitis C genotype 3 patients

Characteristics	SVR (n = 83)	Non-response (n = 36)	Total (n = 119)
Sex			
Male	56 (67.5)	23 (63.9)	79 (66.4)
Female	27 (32.5)	13 (36.1)	40 (33.6)
Age (years)	50.78±9.21	51.58±9.68	51.03±9.32
<40	14 (16.9)	5 (13.9)	19 (16.0)
≥40	69 (83.1)	31 (86.1)	100 (84.0)
BMI (kg/m^2)	24.18±3.34	23.05±3.63	23.84±3.46
<18.5	2 (2.4)	3 (8.3)	5 (4.2)
18.5 to 23.0	32 (38.6)	17 (47.2)	49 (41.2)
23.1 to 27.5	37 (44.6)	13 (36.1)	50 (42.0)
≥27.6	12 (14.5)	3 (8.3)	15 (12.6)
Liver Stiffness, kPa	12.00 (8.00 to 75.00)	17.10 (8.00 to 44.00)	13.00 (8.00 to 75.00)
<12.5	47 (56.6)	6 (16.7)	53 (44.5)
≥12.5	36 (43.4)	30 (83.3)	66 (55.5)
Baseline HCV RNA, IU/mL			
Median	610,089.00	411,500.00	565,305.00
Min-Max	(8,343.00 to 9,750,000.00)	(5,000.00 to 5,354,779.00)	(5,000.00 to 9,750,00.00)
<400,000	41 (49.4)	10 (27.8)	51 (42.9)
≥400,000	42 (50.6)	26 (72.2)	68 (57.1)
Adherence to 80/80/80 rule			
Yes	69 (83.1)	20 (55.6)	89 (74.8)
No	14 (16.9)	16 (44.4)	30 (25.2)
ETR			
Yes	83 (100.0)	16 (44.4)	99 (83.2)
No	0 (0.0)	20 (55.6)	20 (16.8)

SVR = Sustained virological response, BMI = Body mass index, kPa = Kilopascal, ETR = End of treatment response (Undetectable serum HCV RNA at 24 weeks)
Values are represented as n (%), Mean ± SD, Median (min-max)

Table 2. Laboratory of chronic hepatitis C genotype 3 patients

	SVR (n = 83)	Non-response (n = 36)	Total (n = 119)
BUN, mg/dL	11.12±3.15	9.91±3.36	10.75±3.25
Serum creatinine, mg/dL	0.90 (0.5 to 1.4)	0.92 (0.1 to 1.3)	0.90 (0.1 to 1.4)
WBC, cell/mm^3	6,272.77±2,054.48	5,965.00±2,490.00	6,179.66±2,189.14
Hemoglobins, mg/dL	13.36±2.39	13.03±2.27	13.26±2.35
Platelets, cells/mm^3	174,940±63,810	136,190±57,860	163,220±64,360
INR	1.03±0.18	1.10±0.12	1.05±0.17
Serum albumin, g/dL	4.16±0.49	3.86±0.52	4.07±0.52
AST, U/L	69 (18 to 178)	97 (38 to 190)	74 (18 to 190)
ALT, U/L	80 (11 to 350)	92 (34 to 246)	82 (11 to 350)
Total bilirubin, mg/dL	0.63 (0.21 to 3.20)	0.84 (0.10 to 4.65)	0.70 (0.10 to 4.65)
Direct bilirubin, mg/dL	0.26 (0.10 to 3.18)	0.35 (0.10 to 1.62)	0.28 (0.10 to 3.18)

SVR = Sustained virological response, BUN = Blood Urea Nitrogen, WBC = White Blood Cells, INR = International Normalized Ratio, AST = Aspartate aminotransferase, ALT = Alanine aminotransferase
Values are represented as n (%), mean ± SD, median (min-max)

Table 3. Comparison of associated factors of sustained virological response by Chi-square test

	SVR (n = 83)	Non-response (n = 36)	*p*-value
Sex			0.704
Male	56(70.9)	23 (29.1)	
Female	27 (67.5)	13 (32.5)	
Age group, years			0.684
<40	14 (73.7)	5 (26.3)	
≥40	69 (69.0)	31 (31.0)	
BMI, kg/m^2			0.292
<18.5	2 (40.0)	3 (60.0)	
18.5 to 23.0	32 (65.3)	17 (34.7)	
23.1 to 27.5	37 (74.0)	13 (26.0)	
≥27.6	12 (80.0)	3 (20.0)	
Liver Stiffness, kPa			<0.001*
<12.5	47 (88.7)	6 (11.3)	
≥12.5	36 (54.5)	30 (45.5)	
Baseline HCV RNA, IU/mL			0.029*
<400,000	41 (80.4)	10 (19.6)	
≥400,000	42 (61.8)	26 (38.2)	
Adherence to 80/80/80 rule			0.001*
Yes	69 (77.5)	20 (22.5)	
No	14 (46.7)	16 (53.3)	
Peginterferon alfa type			0.575
2a	15 (75.0)	5 (25.0)	
2b	68 (68.7)	31 (31.3)	

SVR = Sustained virological response, BMI = Body mass index, kPa = Kilopascal
Values are represented as n (%), * = Significance at $p<0.05$

12.5 kPa and compliance with the 80/80/80 adherence rule were associated with SVR with adjusted OR of 6.50 (2.24-18.83) and 4.76 (1.64-13.82), respectively.

Discussion

The present study shows the effectiveness of treatment of chronic hepatitis C genotype 3 in real-

Table 4. Multivariate analysis: Odds ratios (OR) for sustained virological response in treated chronic hepatitis C genotype 3 patients

Factors	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Female	0.85 (0.38 to 1.94)	0.704	1.37 (0.48 to 3.91)	0.560
Age <40	1.25 (0.42 to 3.80)	0.684	1.04 (0.26 to 4.17)	0.957
BMI, kg/m^2: 18.5 to 23.0	Reference		Reference	
<18.5	2.82 (0.43 to 18.57)	0.280	1.71 (0.18 to 16.58)	0.646
23.1 to 27.5	4.27 (0.64 to 28.47)	0.134	2.38 (0.24 to 23.78)	0.459
≥27.6	6.00 (0.67 to 53.68)	0.109	2.70 (0.21 to 34.35)	0.443
Liver Stiffness <12.5 kPa	6.53 (2.46 to 17.36)	<0.001*	6.50 (2.24 to 18.83)	0.001*
HCV RNA <400,000 IU/mL	2.54 (1.09 to 5.92)	0.031*	2.19 (0.84 to 5.73)	0.110
Adherence to 80/80/80 rule	3.94 (1.65 to 9.44)	0.002*	4.76 (1.64 to 13.82)	0.004*

BMI = Body mass index, kPa = Kilopascal
Values are represented as median (min-max), * = Significance at $p<0.05$

world practice at Rajavithi Hospital, Thailand. The efficacy of a standard regimen with peginterferon alfa plus ribavirin for 24 weeks achieved SVR in 69.7% of patients, comparable with data from a previous meta-analysis that showed overall SVR at 68%[12]. These satisfactory results can be attributed to the fact that Rajavithi Hospital is a referral tertiary hospital, and patients who come to our institute are expected to adhere to treatment instructions, as witnessed by the impressive (as high as 74.8%) compliance rate with the 80/80/80 adherence rule.

Baseline cirrhosis is a negative factor for treatment response[19,20], and there can be extensive adverse reactions to treatment in this category of patient[21]. In the present study, 55.5% of patients had cirrhosis and 54.5% of them attained SVR, which is a little lower than the general response rate which shows a range of 60% to 80%[12]. Also, most of the patients tolerated this treatment regimen well, confirming that compensated cirrhosis is not a contraindication for treatment[19-22]. Therefore, these patients may be considered as candidate for treatment if they understand about drug toxicity and are closely monitored during follow-up treatment.

Univariate analysis showed that baseline HCV RNA of less than 400,000 IU/mL was associated with SVR, which is in agreement with the findings of a previous study[23]; however, multivariate analysis revealed that the only two parameters that predicted SVR were liver stiffness of less than 12.5 kPa and compliance with the 80/80/80 adherence rule. When implementing the present findings for clinical practice, the optimal time to start treatment of chronic hepatitis C genotype 3 should be as early as possible before patients develop cirrhosis, and a key to achieving high SVR rates is to make the patients aware of the importance of adhering to the 80/80/80 adherence rule. In terms of duration of treatment, extending to 48 weeks does not appear to improve response rates (24 vs. 48 weeks achieved SVR of 48 compared to 42%, respectively)[24]. The present study showed that, in real-world practice, a 24-week treatment duration obtained satisfactory SVR, at 69.7%. Therefore, this regimen should remain a standard treatment for chronic hepatitis C genotype 3 patients in Thailand for now, as DAAs are not available, there are resource constraints, and because this regimen is relatively inexpensive and cost-effective for those who can tolerate peginterferon alfa and ribavirin.

There were several limitations in the present study including its retrospective nature, the small number of patients, and the heterogeneity of peginterferon alfa types and ribavirin doses. Also, the present data represent the treatment efficacy of peginterferon alfa plus ribavirin regimens only in a single tertiary hospital, thus clinical implications may be somewhat limited.

Conclusion

The present study shows that a standard treatment with peginterferon alfa plus ribavirin for 24 weeks in chronic hepatitis C genotype 3 patients is still an effective treatment. Sustained virological response can be improved by selecting patients who are non-cirrhotic for treatment and making them aware of the importance of complying with the 80/80/80 adherence rule. It may be better for cirrhotic patients to wait for new DAAs to avoid unnecessary

exposure to these drugs.

What is already known on this topic?

Chronic hepatitis C genotype 3 is a major public health problem in Thailand, yet few studies about treatment efficacy have been conducted.

A meta-analysis has shown that a standard treatment of chronic hepatitis C genotype 3 patients with peginterferon alfa combined with ribavirin for 24 weeks achieves overall SVR of 68%, with a range of 60% to 80%.

What this study adds?

The treatment efficacy of chronic hepatitis C genotype 3 with peginterferon alfa combined with ribavirin for 24 weeks in Rajavithi Hospital was similar to that found in clinical trials in Western countries.

The present study confirms that being non-cirrhotic and complying with the 80/80/80 adherence rule are predictors of higher sustained virological response rates of patients in Thailand.

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Potential conflicts of interest

None.

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