Original Article

Efficacy of Pegylated Interferon and Ribavirin for the Treatment of Chronic Hepatitis C, Genotype 3 Patients in Thailand

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Objective: Direct-acting antivirals [DAAs] arecurrently widely used for treatment of patients with chronic hepatitis C [CHC]. Few patients are able to access these regimens, especiallyin developing countries. Pegylated interferon [peg-IFN] and ribavirin [RBV] treatment is, therefore, still important. Since 2012, the Thai government has declared peg-IFN and RBV treatment is the standard of care for Thai patients with CHC. The aims of this study were to evaluate the effectiveness of peg-IFN and RBV treatment in CHC, genotype 3 patients in a real-world setting and to determine factors indicating favorable response.

Materials and Methods: This was a retrospective chart review. The data were collected from 30 hospitals in Bangkok and 14 hospitals in Northeastern Thailand during 2012 to 2014. The inclusion criteria were age 18 to 65 years, baseline hepatitis C virus [HCV] viral load [VL] $\geq$5,000 IU/mL, naive to treatment, and at least moderate fibrosis before treatment. Patients with HIV or hepatitis B virus [HBV] co-infection or decompensated cirrhosis were excluded. All patients were treated with peg-IFN and RBV for 24 weeks.

Results: A total of 523 patients were enrolled. The mean age was 48.7$\pm$8.6 years, and 51.6% of patients had age above 50 years. Fifty-two percent were male, and the mean body mass index [BMI] was 24.5$\pm$3.7 kg/m^2. Fifty-eight percent of patients had cirrhosis at baseline. Mean HCV VL was 5.8$\pm$0.8 $\log_{10}$ IU/mL, and 62.1% had HCV VL above 5.6 $\log_{10}$ IU/mL. The mean alanine aminotransferase [ALT] level at baseline was 106.8$\pm$66.5 U/L, and the mean platelet count was 158,000$\pm$65,900/mm^3. The overall prevalence of sustained virological response [SVR] was 74.6%. The prevalences of SVR in patients with cirrhosis and without cirrhosis were 66.8% and 84%, respectively (p<0.001). Factors determining good response were noncirrhosis, HCV VL <5.6 $\log_{10}$ IU/mL at baseline, age <50 years, no reduced dose of peg-IFN during treatment, and platelet count >150,000/mm^3. Multivariate analysis, however, demonstrated that factors indicating favorable response were age <50 years, no cirrhosis, and HCV <5.6 $\log_{10}$ IU/mL at baseline.

Conclusion: The effectiveness of peg-IFN and RBV for treatment of patients with CHC, genotype 3 was good. Patients with old age, cirrhosis, and high HCV VL at baselinetended to have treatment failure. DAAsmay be considered as the first treatment for patients with these factors.

Keywords: Hepatitis C, Real-world, Interferon, Ribavirin, Genotype 3

J Med Assoc Thai 2018; 101 [Suppl. 4]: S127-S134
Website: http://www.jmatonline.com

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How to cite this article: Chotiyaputta W, Kaosombatwattana U, Chamroonkul N, Bunchorntavakul C, Seansawat K, Techathunvanan K, Apisophonsiri P, Tanwandee T. Efficacy of PegylatedInterferon and Ribavirin for the Treatment of Chronic Hepatitis C, Genotype 3 Patients in Thailand. J Med Assoc Thai 2018;101;Suppl.4:S127-134.

Chronic hepatitis C [CHC] is one of major causes of cirrhosis and hepatocellular carcinoma [HCC]. The goal of CHC treatment is to cure the disease or a sustained virological response [SVR]. After eradication of the disease, overall mortality, liver-related mortality, progression to liver failure, and progression to HCC were decreased[1].The treatment of CHC is,therefore,cost-effective. In recent years, many direct-acting antivirals [DAAs] have been rapidly developed to enhance the efficacy of treatment. Because DAAs have easy drug administration, few side effects, a short duration of treatment, and high efficacy, many recommendations about the treatment for CHC patients have changed from a combination of pegylated interferon [peg-IFN] and ribavirin [RBV] to DAAs regimens[2-4]. One major barrier of using DAAs is, however, the cost of treatment. Many patients have not been able to access DAAs, especially thoseliving in developing countries. The combination of peg-IFN with RBVis still being used in many developing countries where resources are limited. Although the efficacy of peg-IFN and RBV is good for genotypes 2 and 3, the success of treatment for genotype 1 is poor (only 21 to 54%)[5-8]. One pivotal obstacle for treatment with peg-IFN and RBV is its many side effects[5]. This regimen is, however, cheaper than DAAs regimens, and many patients have been able to access the combination of peg-IFN and RBV. Since 2012, the Thai government has considered the importance of treating CHC patients to prevent progression to end-stage liver disease, decrease the overall and liver-related mortality, as well as improve theirquality of life. The Thai government has declared the combination of peg-IFN and RBV as thestandard treatment, and it is universally accessible for all Thai CHC patients without any payment. The Thai government,nevertheless, has set treatment eligibility criteria for CHC patients. The criteria are male or female, age 18 to 65 years, naive to treatment, moderate degree of liver fibrosis using either liver biopsy (METAVIR fibrosis score ≥2) or transient elastrography ≥7.5 kPa), hepatitis C virus [HCV] viral load [VL] at baseline ≥5,000 IU/mL, and no existing malignancies. In addition, patients should have had abstinence from drinking alcohol for at least 6 months, no hepatitis B virus [HBV] or HIV co-infection, and compensated liver condition. This policy began in patients infected with genotype 3 because it was the most common genotype in Thailand[9].

The aims of this study were to determine the efficacy of peg-IFN and RBV for treatment CHC genotype 3 in a real-world setting and to identify which factors determine a favorable outcome.

Materials and Methods

This was a retrospective chart review of CHC, genotype 3 patients who were treated between 2012 and 2014 according to the Thai government policy. The data were collected from 30 hospitals in Bangkok and 14 hospitals in Northeastern Thailand. All patients were treated with either peg-IFN alpha 2a (Pegasys™) 180 mcg once a week and RBV (Copegus™) 800 mg/day or peg-IFN alpha 2b (Peg-intron) 1.5 mcg/kg once a week and RBV (Rebetol™) 800 mg/day for 24 weeks. Cirrhosis was defined as a liver fibrosis METAVIR score of F4 or liver stiffness of ≥12.5 kPa. SVR was defined as undetectable HCV RNA VL at 24 weeks after treatment using a highly sensitive polymerase chain reaction technique. Baseline characteristics including age, gender, weight, height, underlying medical diseases (e.g. hypertension, diabetes, dyslipidemia, ischemic heart disease, stroke), and the degree of liver fibrosis were collected. Baseline HCV RNA VL and lab test data were retrieved, and the data of medications and level of treated hospital were divided to two groups according tothe area in which each participating hospital is located, namely eitherthe Bangkok area or Northeastern Thailand.

Data were analyzed by PASW Statistics for Windows version 18.0 (SPSS Inc, Chicago, IL). Categorical data were presented as percentage, and continuous data was presented as mean and standard deviation [SD]. Comparison of categorical variables was analyzed with the χ^2 test, and continuous variables were analyzed with the ANOVA F-test. Statistical significance was determinedin a two-tailed analysis with a *p*-value of ≤0.05 considered statistically significant.

Results

A total of 608 patients were eligible for this study. Sixty-eight patients had been treated for 24 weeks but were lost-to-follow-up after completing treatment. Seventeen patients (2.8%) were not able to complete the treatment due to intolerance to side effects. The data of the remaining 523 patients was, therefore, retrieved for analysis. Two hundred and ninety-one patients were treated in hospitals in Bangkok, and 232 patients were treated in hospitals in Northeastern Thailand.

Baseline characteristics of patients

The mean age was 48.7 years (SD 8.6 years),

and 67% were male. Compared with the Northeastern Thailand group, significant differences in patients in the Bangkok group wereolder age, a greater percentage of males, and higher body mass index [BMI]. Patients in the Bangkok group also had significantly more underlying diseases compared with the Northeastern Thailand group. The mean baseline HCV RNA VL of all patients was 5.84 $\log_{10}$ IU/mL (SD 0.83), and prevalence of patients with HCV RNA VLof more than 5.6 $\log_{10}$ IU/mL was 62.1%. Of all patients,70% were evaluated for liver fibrosis by transient elastrography, 12% were assessed by liver biopsy, and 12% were assessed by both methods. Although liver fibrosis assessment must be evaluated before treatment, 6.4% of patients had had neither transient elastrography nor liver biopsy performed. The prevalence of patients with cirrhosis at baseline was 57.9%, and the prevalence of cirrhotic patients in the Bangkok area and Northeastern Thailand were similar. Laboratory tests at baseline, including hemoglobin level, platelet count, total bilirubin, albumin, aspartate aminotransferase [AST], and alanine aminotransferase [ALT] were not significantly different between the Bangkok group and Northeastern Thailand group (Table 1).

Table 1. Baseline characteristics

	Bangkok (n = 291)	Northeastern Thailand (n = 232)	Total (n = 523)	*p*-value
Age (year)	49.8±9.1	47.4±7.7	48.7±8.6	0.001
≥50 years	170 (58.4)	100 (43.1)	270 (51.6)	<0.001
Male gender	180 (61.9)	171 (73.7)	351 (67.1)	0.004
BW (kg)	66.5±12.9	65.1±10.6	65.9±11.9	0.19
Height (cm)	163.5±8.3	164.2±8.0	163.8±8.2	0.37
BMI (kg/m^2)	24.9±3.9	24.0±3.4	24.5±3.7	0.008
Level of hospital				
University	150 (51.5)	124 (53.4)	274 (52.4)	<0.001
Tertiary	92 (31.6)	108 (46.6)	200 (38.2)	
Private	49 (16.8)	0	49 (9.4)	
Underlying diseases	107 (36.8)	39 (16.8)	146 (27.9)	<0.001
Type of fibrosis evaluation				
Liver biopsy	39 (13.4)	24 (10.3)	63 (12)	<0.001
Transient elastography	209 (71.8)	155 (66.8)	364 (69.6)	
Both	19 (6.5)	44 (19)	63 (12)	
None	24 (8.3)	9 (3.9)	33 (6.4)	
Cirrhosis	155/266 (58.3)	128/223 (57.4)	283/489 (57.9)	0.85
Type of peg-IFN				
2a	172 (59.1)	102 (44)	274 (52.4)	0.01
2b	119 (40.9)	130 (56)	249 (47.6)	
Reduced dose of peg-IFN	45/280 (16.1)	9/213 (4.2)	54/493 (11)	<0.001
Reduced dose of RBV	57/276 (20.7)	11/213 (5.2)	68/489 (13.9)	<0.001
HCV VL at baseline($\log_{10}$ IU/mL)	5.86±0.82	5.81±0.85	5.84±0.83	0.52
HCV VL ≥5.6$\log_{10}$IU/mL	190 (65.3)	135 (58.2)	325 (62.1)	0.10
Hemoglobin (g/dL)	14.2±3.7	14.0±2.7	14.1±3.3	0.52
WBC ($cells/mm^3$)	6,243±2,684	6,399±1,756	6,311±2,327	0.47
Platelet count (x $10^3/mm^3$)	161.9±67.8	153.0±63.1	158.0±65.9	0.15
Total bilirubin (mg/dL)	0.9±0.9	0.8±0.8	0.9±0.8	0.11
AST (U/L)	96.0±61.3	104.9±119.3	100.5±94.9	0.32
ALT (U/L)	105.9±70.1	107.9±61.7	106.8±66.5	0.74
Albumin (g/dL)	4.3±2.9	4.2±1.9	4.3±2.5	0.61

BW = body weight; peg-IFN = pegylated interferon; RBV = ribavirin; HCV VL = hepatitis C viral load; WBC = white blood cell count; AST = aspartate aminotransferase; ALT = alanine aminotransferase
Data were expressed as mean ± SD or number (%).

Type of medications and reduced dose of medications during treatment

Of all patients, 52.4% had been treated with peg-IFN alpha 2a, and 47.6% had been treated with peg-IFN alpha 2b. Of the patients in the Bangkok group, 59% were treated with peg-IFN alpha 2a whereas 56% of the patients in the Northeastern Thailand group were treated with peg-IFN alpha 2b (p = 0.01). During treatment, 16.1% of patients in the Bangkok group had a reduced dose of peg-IFN, and 20.7% had a reduced dose of RBV. In contrast, 4.2% of patients in the Northeastern Thailand group had a reduced dose of peg-IFN, and 5.2% had a reduced dose of RBV with statistical significanceas shown in Table 1 (p<0.001 and p<0.001, respectively).

Sustained virological response [SVR]

The prevalence of SVR in all patients was 74.6%. The prevalences of SVR of patients in the Bangkok group and Northeastern Thailand group were 71.5% and 78.4%, respectively (Table 2). Patients in the Bangkok group tended to have a lower prevalence of SVR than patients in the Northeastern Thailand group (p = 0.07) (Table 2). The prevalence of SVR in patients with cirrhosis was 66.8%, and the prevalence of SVR of those without cirrhosis was 84%. It was statistically significant (p<0.001) as shown in Figure 1.

Predictors of favorable response to treatment

Multiple factors including baseline characteristics, underlying cirrhosis, viral factors, and treatment factors were analyzed to find to predictors of treatment outcome. Factors at baseline that predicted a good response to peg-IFN and RBV treatment were younger age, noncirrhosis, lower HCV VL, higher platelet count, and no reduced dose of peg-IFN during treatment (Table 3). All of these factors were included in multivariate analysis. Age below 50 years, noncirrhosis, and HCV below 5.6 $\log_{10}$ IU/ml were significant predictors of favorable response to treatment (Table 3).

Flow chart of predicted response

Important baseline factors that predicted a favorable response by multivariate analysis were analyzed to predict the response of treatment. These baseline factors were baseline HCV RNA VL below or above 400,000 IU/mL, the presence or absence cirrhosis, and age below or above 50 years of age. A proposed flow chart of predicted response is shown in Figure 2. The best response to treatment was in a patient who had HCV RNA VL less than 400,000 IU/mL, the absence of cirrhosis, and age less than 50 years old, which predicted a rate of SVR of 92.7%. The worst response of treatment was, conversely, a patient who had HCV RNA VL above 400,000 IU/mL, the presence of cirrhosis, and age more than 50 years, which predicted a rate of SVR of approximately 50%.

Discussion

The prevalence of hepatitis C infection is approximately 1% in Thailand, and the most common genotype is genotype 3[9]. The Thai government has implemented the policy for all Thai people infected with HCV to receive treatment with peg-IFN and RBV since 2012. The policy began in patients with genotypes 2 and 3, followed by genotypes 1 and 6. The aims of this study were to assess the efficacy and the safety of peg-IFN and RBV in the treatment of CHC genotypes 2 and 3 in a real-world setting; no patients with genotype 2 were enrolled in this study.

The study was investigated in only 2 areas of Thailand because more than 50% of Thai patients had been treated in those areas. Most patients were middle aged, male gender, and sthenic build. Approximately 95% of patients were evaluated for liver fibrosis before treatment, which demonstrated 58% of patients had cirrhosis. The high percentage of cirrhotic patients in this study was due to the long waiting period that many patients had experienced before this policy started. Only a few patients (not more than 3%) were intolerant to the side effects of the treatment although more than 50% of patients were cirrhosis, which is a condition with potentially more side effects of treatment.

The overall prevalence of SVR was 74.6%, which was similar with previous studies[8,10-12]. Patients in the Northeastern Thailand group had a higher prevalence of SVR compared with the Bangkok group; however, it was not statistically significant. Plausible explanations mightbe that patients in the Northeastern Thailand group had younger age, lower BMI and fewer underlying medical conditions compared with the Bangkok group. Another important possibility was that a reduced dose of peg-IFN or RBV during the treatment was less common in the Northeastern Thailand group. A reduced dose of peg-IFN or RBV during treatment was the pivotal factor that decreased the rate of SVR as demonstrated in previous studies. The patients were divided to 2 groups according to the presence of cirrhosis. The SVR of patients who did not have cirrhosis was significantly higher than those who had cirrhosis (84% vs. 66.8%). The degree of liver fibrosis was a

Table 2. Factors associated with sustained virological response

Predictors	SVR (n = 390)	No SVR (n = 133)	*p*-value
Gender			
Male	268 (68.7)	83 (62.4)	0.18
Female	122 (31.3)	50 (37.6)	
Age			
<50 years	204 (52.3)	49 (36.8)	0.002
≥50 years	186 (47.7)	84 (63.2)	
Body weight (kg)	65.7±11.9	66.4±12.0	0.56
Height (cm)	164.0±8.4	163.4±7.5	0.52
BMI (kg/m^2)	24.3±3.7	25.0±3.6	0.07
Area of residence			
Bangkok	208 (53.3)	83 (62.4)	0.07
Northeast	182 (46.7)	50 (37.6)	
Level of hospital			
University	205 (52.6)	69 (51.9)	0.89
Tertiary	150 (38.5)	50 (37.6)	
Private	35 (8.9)	14 (10.5)	
Underlying diseases	101 (25.9)	45 (33.8)	0.08
Cirrhosis	189 (48.5)	94 (70.7)	<0.001
Type of peg-IFN			
2a	204 (52.3)	70 (52.6)	0.95
2b	186 (47.7)	63 (47.4)	
Reduced dose of peg-IFN	34/366 (9.3)	20/127 (15.8)	0.05
Reduced dose of ribavirin	48/364 (13.2)	20/125 (16.0)	0.43
HCV VL at baseline (IU/mL)			
<5.6 log_{10}	167 (42.8)	31 (23.3)	<0.001
≥5.6 log_{10}	223 (57.2)	102 (76.7)	
Hemoglobin (g/dL)	14.1±3.4	14.0±3.0	0.60
WBC ($cells/mm^3$)	6,225±1,838	6,551±3,333	0.30
Platelet count ($x10^3/mm^3$)			
<150	152/344 (44.2)	77/123 (62.6)	<0.001
≥150	192/344 (55.8)	46/123 (37.4)	
AST (U/L)	100.0±106.1	101.7±49.3	0.87
ALT (U/L)	105.7±67.4	109.8±64.1	0.55
Albumin (g/dL)	4.3±2.4	4.2±3.0	0.91
Total bilirubin (mg/dL)	0.8±0.9	1.0±0.5	0.16

BMI = body mass index; peg-IFN = pegylated interferon; HCV VL = hepatitis C viral load; WBC = white blood cell count; AST = aspartate aminotransferase; ALT = alanine aminotransferase; SVR = sustained virological response
Data are expressed as mean ± SD or number (%).

major factor for the lower prevalence of SVR in the present study, which was similar with previous studies[10,11].

On multivariate analysis, 3 factors which determined better SVR were identified. These factors were age less than 50 years old, the absence of cirrhosis, and a low VL at baseline (below 400,000 U/mL). These have been well accepted as good prognostic factors from previous studies[10,11,13]. Other factors such as platelet count at baseline and reduced dose of peg-IFN during treatment were not important factors on multivariate analysis although they were significant on univariate analysis. This data illustrates that reduced dose of peg-IFN had a trend to bebarrier for success of treatment; however, it did not show significance on multivariate analysis. Even though reduced dose of peg-IFN or RBV was a major obstacle for SVR to treatment in previous studies[14,15], the data of the present real-world study did not confirm this as an obstacle. This data implies that a reduced dose of the

Table 3. Univariate and multivariate analyses of factors associated with sustained virological response

Predictors	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
No cirrhosis	2.61	1.67 to 4.08	<0.001	2.54	1.6 to 4.03	<0.001
HCV viral load <5.6 $\log_{10}$	2.46	1.57 to 3.86	<0.001	2.86	1.75 to 4.53	<0.001
Age <50 years	1.88	1.26 to 2.82	0.002	1.64	1.06 to 2.53	0.03
No reduced dose of peg-IFN	1.83	1.26 to 2.82	0.05	-	-	NS
Platelet count ≥150x10^3/mm^3	2.11	1.39 to 3.23	<0.001	-	-	NS

HCV = hepatitis C virus; peg-IFN = pegylated interferon; NS = not significant

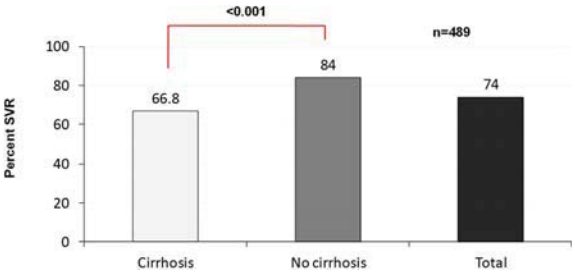
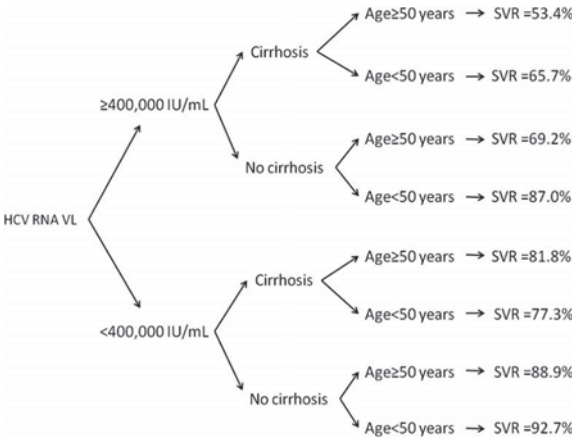


Figure 1. Comparison between sustained virological response in patients with or without cirrhosis.



HCV = hepatitis C virus; VL = viral load; SVR = sustained virological response

Figure 2. Flow chart for predicted response to treatment.

medications should be performed in patients who were not able to tolerate the side effects of the medications regardless of the outcome of treatment.

Three important factors were used to make a flow chart to predict the treatment response. A CHC, genotype 3 patient with an age less than 50 years old, a low VL at baseline, and no cirrhosis is predicted to have the highest rate of SVR (92.7%). In contrast, a patient with an age more than 50 years old, a high VL at baseline, and cirrhosis is predicted to have the lowest SVR rate (53.4%).

Currently, treatment for CHC has been changed from a combination of peg-IFN and RBV to an oral interferon-free regimen. The efficacy of DAAs is very impressive with fewer side effects. In Germany, the regimen for treatment hepatitis C has changed enormously between 2011 and 2016[16]. The cost of treatment is, however, the major barrier for access formany hepatitis C infected patients in developing countries. Peg-IFN and RBV is still a good alternative treatment for resource-limited countries. Patients with poor prognostic factors, however, have unacceptable rates of SVR such as patients with an age more than 50 years, a high VL at baseline, and cirrhosis (rate of SVR predicted to be approximately 53%). If we consider an SVR rate of more than 70% to be acceptable, patients with high VL and cirrhosis should not be treated with peg-IFN and RBV. These patients should be recommended treatment with DAAs. On the other hand, patients with low VL at baseline regardless of cirrhosis or patients with high VL at baseline and no cirrhosis can be treated with peg-IFN and RBV as the first line treatment of CHC.

This study had the strength of reflecting multiple real-world clinical practice settings. The data were collected from multiple hospitals and many physicians, and all physicians who treated all of these patients had to be gastroenterologists. All patients varied in baseline characteristics and clinical symptoms. Some patients were asymptomatic at presentation, but some patients presented as nearly

decompensate dcirrhosis. Methods of treatment, patterns of monitoring patients, and patterns of reduced dose of medications also varied according to clinical practices of physicians. The data of this study is, therefore, totally different from the setting of a phase 3 clinical trial. This study also has some limitations. First, this study was a retrospective study. There are limits of data about baseline characteristics, side effects of medications during treatment, and the data of the amount of reduced dose of peg-IFN and RBV. Second, there are no data about rapid virological response and early virological response from VL during treatment. Third, there are no data about the IL28B phenotype, which is an important factor for the outcome of peg-IFN treatment in CHC-infected patients.

Conclusion

The peg-IFN and RBV regimen hasgood efficacy for treatment CHC, genotype 3 patients with a good safety profile. This regimen is still acceptable for the first line treatment in resource-limited countries; however, this regimen should not be used in patients who have high VL and cirrhosis at baseline. DAAs regimen should be considered for these patients.

What is already known on this topic?

Pegylated interferon [peg-IFN] and ribavirin [RBV] is still treatment regimen for chronic hepatitis C [CHC]-infected patients, especially in developing countries where resources are limited. The efficacy of peg-IFN and RBV treatment for CHC, genotypes 2 and 3 is good However, the efficacy of peg-IFN and RBV treatment for other genotypes is disappointing.

What this study adds?

This study provides the prevalence of sustained virological responseof peg-IFN and RBV treatment for CHC, genotype 3 in Thai patients. The major factors at baseline determining favorable response are age <50 years, hepatitis C viral load <400,000 IU/mL, and noncirrhosis. CHC, genotype 3-infected patients with older age, high viral load, and cirrhosis at baseline should be treated with DAAs instead of peg-IFN and RBV.

Acknowledgements

The research was supported by a grant from Thai National Health Security Office.

Potential conflicts of interest

None.

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