Response to Treatment of Chronic Hepatitis C Infection Genotypes 1 and 6 with Peginterferon Alfa Plus Ribavirin in Rajavithi Hospital

Siam Sirinthornpunya MD*, Thanaya Techasiriaongkun RN*

** Division of Gastroenterology and Hepatology, Department of Medicine, Rajavithi Hospital, Ministry of Public Health, College of Medicine, Rangsit University, Bangkok, Thailand*

Background: *Chronic hepatitis C (CHC) genotypes 1 and 6 are common in Thailand and often cause cirrhosis and other complications. Treatment with peginterferon alfa plus ribavirin is currently still recommended, but it has limited efficacy, entails long duration of treatment, and results in some adverse side effects. New direct-acting antiviral agents (DAAs) are effective treatments, but they are costly and not readily available.*

Objective: *To evaluate the response of CHC genotypes 1 and 6 to treatment with peginterferon alfa plus ribavirin, and to find the predictive factors of treatment response.*

Material and Method: *Data were collected retrospectively from patients with chronic Hepatitis C genotypes 1 and 6 who were treated with peginterferon alfa plus ribavirin for 48 weeks between 2013 and 2016 at Rajavithi Hospital, Bangkok. Demographic information and laboratory data were recorded, together with details of virological data, treatment response, and treatment compliance with the 80/80/80 rule. Data analysis was performed of treatment response and its predictive factors.*

Results: *Seventy-one patients with a mean age 50.76±9.70 years were included, of which 71.8% were men, 55.0% were genotype 1, and 45.0% were genotype 6. Eighty-three percent of patients were aged more than 40 years, 67.6% had body mass index less than 25kg/m^2, 53.5% had cirrhosis, and Hepatitis C RNA levels (HCV RNA level) of more than 400,000 iu/ml were found in 78.9% of cases. The overall Sustained Virological Response (SVR) rate was 77.5%, while genotypes 1 and 6 had SVR of 79.5% and 75%, respectively. SVR was associated with people aged more than 40 years old (p = 0.022), high baseline ALT level (p = 0.006), virological response during treatment at 12 and 24 weeks and at end of treatment (EOTR) (p = 0.019, 0.011 and 0.002 respectively), and treatment compliance (p<0.001). Multivariate analysis found that treatment compliance with the 80/80/80 rule was the only factor associated with SVR OR = 31.5, 95% CI (6.16 to 161.15).*

Conclusion: *Response of CHC genotypes 1 and 6 to treatment with peginterferon alfa plus ribavirin was good. Selection of suitable patients and good compliance with treatment resulted in high SVR rates, comparable to those achieved with DAA regimens.*

Keywords: *Chronic hepatitis C, Genotype 1, Genotype 6, Treatment response, Sustained virological response, HCV RNA level, Transient elastography, Peginterferon alfa, Ribavirin*

J Med Assoc Thai 2018; 101 (Suppl. 2): S45-S52
Full text. e-Journal: *http://www.jmatonline.com*

Chronic hepatitis C (CHC), chronic liver inflammation caused by the Hepatitis C virus, is developed by 50 to 80% of Hepatitis C patients, and is a common cause of cirrhosis and hepatocellular carcinoma worldwide. Most patients are asymptomatic, about 20 to 50% develop cirrhosis within 20 years[1-4] and 20% of patients develop hepatocellular carcinoma. Worldwide, 175 million people are infected by this virus and 3 to 4 million people are newly infected with HCV every year; furthermore, over 350,000 people die from HCV-related liver disease each year[5-7].

The Hepatitis C virus is classified into six major genotypes, and there are significant geographic patterns in their respective prevalence rates. Genotypes 1, 2 and 3 are most common in Asia, Europe and America, while genotype 4 is typically found in the Middle East and Africa, and genotypes 5 and 6 tend to be most prevalent in South Africa and Southeast Asia, respectively[8]. Genotype is an important factor in predicting treatment response for hepatitis C

Correspondence to:
Sirinthornpunya S, Division of Gastroenterology, Department of Medicine, Rajavithi Hospital, 2 Phyathai Road, Ratchathewi, Bangkok 10400, Thailand.
Phone: +66-2-3548108 ext. 5101
E-mail: s_sirinthorn@yahoo.com

infection[9].

In Thailand, the prevalence of HCV infection is about 1 to 2%. HCV genotype distribution shows that HCV genotype 3a is most common (33.3 to 36.7%), followed by genotypes 6 (29.4 to 31.0%), 1a (14.3 to 19.3%), 1b (6.4 to 12.7%) and 3b (5.6 to 6.3%)[10].

Current treatment for CHC is rapidly changing. In the past, a combination of pegylated interferon plus ribavirin was used, but it was only moderately effective (50 to 80% responsiveness) and produced several adverse side effects. Combinations of direct acting antiviral agents (DAAs) show more potent efficacy and produce fewer side effects, but they are still very costly[11,12]. Owing to problems related to drug availability and budget limitations, the national policy for CHC is still to use combinations of pegylated interferon plus ribavirin for standard treatment.

Indications for treatment of CHC with pegylated interferon plus ribavirin in Thailand include moderate liver fibrosis (METAVIR score ≥F2 or fibro scan value >7.5 kPa) and nocompensated cirrhosis[13]. The target of treatment is sustained virological response (SVR) which is defined as non-undetectable levels of HCV RNA 24 weeks after completion of treatment[12,14]. In a study reported in 2010, most patients (99.1%) who achieved an SVR had undetectable levels of HCV RNA in serum samples throughout the follow-up period of 3.9 years and these patients should be considered as cured[15]. The achievement of SVR in patients with CHC has been associated with reduced risk of cirrhosis, complications, hepatocellular carcinoma (HCC) and liver-related mortality[16].

Sustained virological response (SVR) rates in patients with hepatitis C are influenced by host factors (such as age, gender, duration of HCV infection, alcohol intake, hepatic iron stores, platelet count, and histological staging of the liver disease), viral factors (HCV RNA levels in serum, HCV genotype) and treatment factors (dose, duration and type of treatment regimens)[9,17]. Most research has shown that the treatment response rates of CHC patients in Asian countries are better than those of patients in Europe and America[11,18].

In patients with genotypes 1 and 6, the duration of treatment is 48 weeks, which is longer than in patients with genotypes 2 or 3. Sustained virological response rates 24 weeks after the end of treatment (SVR) for patients with Hepatitis C genotypes 1 and 6 are about 42 to 52% and 60 to 90%, respectively, and these rates are less impressive than SVR of patients with genotype 3 infection[19-22]. Although better treatment response rates are achieved by DAAs in patients with genotypes 1 and 6, availability limitations and budget constrictions result in peginterferon alfa plus ribavirin being recommended in Asia and Europe for treatment of CHC in settings where DAAs are not accessible[11,23]. The present study examined the response rates of CHC to genotype 1 are treatment with pegylated interferon plus ribavirin and factors that affect the treatment outcomes in order to determine the future direction of treatment to improve patient care.

Material and Method

Patients

This retrospective study was conducted between 2013 and 2016 in Rajavithi Hospital, Bangkok, Thailand. CHC patients genotypes 1 and 6, aged 18-65 years who had moderate liver fibrosis (METAVIR ≥F2 or fibro scan ≥7.5 kPa) and nocompensated cirrhosis received antiviral therapy with pegylated interferon plus ribavirin for 48 weeks.

Inclusion criteria for treatment were based on the Thailand National Guidelines for treatment of CHC: ECOG performance status 0 to 1; HCV-DNA >5,000 IU/mL; significant fibrosis (METAVIR SCORE >F2 or fibrosis value >7.5 kPa); and non-decompensated cirrhosis. Diagnosis of decompensated cirrhosis was based on clinical and laboratory findings such as anemia, jaundice, hepatic encephalopathy or portal hypertension (ascites, splenomegaly, superficial vein dilatation and esophageal varices). The laboratory results suggestive of decompensated cirrhosis were thrombocytopenia (platelets <100,000/mm^3), low serum albumin (<3.5 gram/dl) and prolonged prothrombin time (>13 seconds or INR >1.2). Exclusion criteria were patients with allergies to interferon or ribavirin, uncontrolled major depression, pregnancy or unwillingness to practice birth control, or who had undergone organ transplantation, had uncontrolled underlying diseases such as hypertension, diabetic mellitus, heart disease, hyperthyroidism, chronic alcoholism, treatment with chemotherapy or drug addiction. This study protocol was reviewed and approved by the ethics committee of Rajavithi Hospital (No. 093/2560).

Methods

Demographic information, physical examination data and biochemical results (e.g. complete blood count, liver function, prothrombin time and INR), transient elastography and RNA viral loads were collected at baseline. Patients received either 180 ug

peginterferon alfa 2a or 1.0 to 1.5 ug/kg peginterferon alfa 2b subcutaneous injection (SC) once per week plus ribavirin 800 to 1,400 mg/day (depending on patient body weight) for 48 weeks. Complete blood count and liver function tests were followed-up and HCV RNA levels were evaluated at week 12, week 24, end of treatment and 24 weeks after complete treatment. Treatment compliance with the 80/80/80 rule was fulfilled when patients received at least 80% of each drug for at least 80% of the treatment duration.

Treatment response definition

End of treatment response (EOTR) was defined as the inability to detect HCV RNA in serum at the end of treatment.

Sustained virological response (SVR) was defined as the inability to detect HCV RNA in serum 24 weeks after completion of treatment.

Statistical analysis

Continuous variables of demographic data were presented as mean $\pm$ SD in normal distribution data or median (min-max) in non–normal distribution data while categorical variables were given as number with percentage. Continuous variables were compared using t-test or the Mann-Whitney U test in non–normal distribution data, and categorical variables were compared using the Chi-square test or Fisher exact test. Multiple logistic regression analysis was used to determine the factors affecting SVR. Results were described as Odds ratio (OR) with 95% confidence intervals, and a p-value of less than 0.05 was considered statistically significant. Data were analyzed using SPSS software version 17.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Demographic data

Seventy-one patients were included: 71.8% (51/71) were men, 55.0% (39/71) were genotype 1, 45.0% (32/71) were genotype 6 and their mean age was 50.76$\pm$9.70 years. Most patients (83.1%) were aged more than 40 years, 53.5% had cirrhosis (transient elastography >12.5)[24], 67.6% had body mass index less than 25 kg/m^2, 78.9% had HCV RNA level more than 400,000 iu/ml, and 69% received treatment with peginterferon alfa 2b plus ribavirin. The baseline characteristics of CHC patients genotypes 1 and 6 were not significantly different, and the baseline laboratory data of the two genotypes were also not significantly different except that more thrombocytopenia (platelet count less than 100,000 cell/ml) was found in patients with genotype 6 (0% in genotype 1 and 21.9% in genotype 6, p = 0.003). Baseline demographic and laboratory data are summarized in Table 1 and 2.

Treatment response and its predictors

SVR in patients overall, genotype 1 and genotype 6 were 77.5% (55/71), 79.5% (31/39) and 75.0% (24/32), respectively. Number of host and viral factors were associated with achieving SVR. SVR was associated with patients aged more than 40 years (p = 0.022), high baseline ALT levels (87 in SVR group and 46 in non-SVR group, p = 0.006), virological response during treatment at 12, 24 weeks and at end of treatment (EOTR) (p = 0.019, 0.011 and 0.002 respectively) and treatment compliance (95.7% in SVR group and 41.7% in non-SVR group, p<0.001) (Table 3).

Multivariate analysis found that only treatment compliance with the 80/80/80 rule was associated with SVR with OR = 31.5, 95% CI: 6.16 to 161.15, p = 0.003. Other factors were not statistic significant associated with SVR (Table 4).

Discussion

SVR rates of CHC genotypes 1 and 6 in the present study were 79.5% and 75.0%, respectively. These results are better than those found in research in Western countries (42 to 52% in genotype 1 and 61 to 70% in genotype 6)[19-22], but they are comparable with the results of studies in Asian countries (61 to 79% in genotype 1 and 69 to 76% in genotype 6)[18]. The present study showed that the SVR of patients with CHC genotype 1 was better than that of genotype 6 patients, and this is at variance with the findings of other studies[25,26]. These results may have been affected by the different levels of severity of liver disease or cirrhosis (transient elastography >12.5 in 65.6% in genotype 6 and 43.6% in genotype 1), and there was more evidence of portal hypertension in patients with genotype 6 (thrombocytopenia 21.9% in genotype 6 and 0% in genotype 1).

Our study reviewed multiple factors associated with SVR such as age group, ALT level, virological response at 12 and 24 weeks during treatment, end of treatment and treatment compliance. Age has been shown in many studies to be associated with SVR, as young patients have higher rates of SVR than older ones[27,28]. However, some studies have found that age is not a negative predictive factor for SVR, which is different from the findings of our research[29,30]. The present study indicated that peginterferon plus

Table 1. Demographic and clinical data of chronic hepatitis C (n = 71)

Factors	Total (n = 71)	Genotype 1 (n = 39)	Genotype 6 (n = 32)	*p*-value
Sex				0.994
Male	51 (71.8)	28 (71.8)	23 (71.9)	
Female	20 (28.2)	11 (28.2)	9 (28.1)	
Age (years)	50.76±9.70	51.05±10.01	50.41±9.46	0.783
≤40	12 (16.9)	6 (15.4)	6 (18.8)	0.707
>40	59 (83.1)	33 (84.6)	26 (81.2)	
BMI (kg/m^2)	23.51±3.66	23.46±3.74	23.56±3.61	0.914
<25	48 (67.6)	26 (66.7)	22 (68.8)	1.000
25 to 29.99	20 (28.2)	11 (28.2)	9 (28.1)	
≥30	3 (4.2)	2 (5.1)	1 (3.1)	
Liver Stiffness (kPa)				0.064
<12.5	33 (46.5)	22 (56.4)	11 (34.4)	
≥12.5	38 (53.5)	17 (43.6)	21 (65.6)	
HCVRNA (IU/mL)				0.191
<400,000	15 (21.1)	6 (15.4)	9 (28.1)	
≥400,000	56 (78.9)	33 (84.6)	23 (71.9)	
Type of Peg interferon				0.576
α2a	22 (31.0)	11 (28.2)	11 (34.4)	
α2b	49 (69.0)	28 (71.8)	21 (65.6)	

BMI = Body mass index, HCVRNA = Hepatitis C virus RNA level
Values are presented as n (%), mean±SD, * = Significant at $p<0.05$

Table 2. Laboratory data of patients with chronic hepatitis C (n = 71)

Factors	Total (n = 71)	Genotype 1 (n = 39)	Genotype 6 (n = 32)	*p*-value
Hemoglobins (g/dL)	13.71±1.82	13.58±1.75	13.86±1.92	0.531
WBC (cell/mm^3)	6,850.00±1,792.54	6,894.87±1,556.64	6,795.31±2,068.75	0.818
Platelets (cell/mm^3)				0.003*
≤100,000	7 (9.90)	0 (0.0)	7 (21.9)	
>100,000	64 (90.10)	39 (100.0)	25 (78.1)	
Serum albumin (g/dL)	4.24±0.42	4.22±0.33	4.27±0.52	0.596
Total bilirubin (mg/dL)	0.65 (0.19 to 3.13)	0.66 (0.23 to 2.10)	0.63 (0.19 to 3.13)	0.703
Direct bilirubin (mg/dL)	0.29 (0.10 to 1.18)	0.29 (0.11 to 1.05)	0.27 (0.10 to 1.18)	0.592
AST (U/L)	71.00 (23.00 to 225.00)	71.00 (28.00 to 225.00)	67.00 (23.00 to 187.00)	0.646
ALT (U/L)	85.00 (20.00 to 380.00)	92.00 (25.00 to 224.00)	82.50 (20.00 to 380.00)	0.909
INR	1.07±0.12	1.08±0.13	1.06±0.09	0.394
BUN (mg/dL)	10 (6.00 to 112.00)	10 (6.00 to 112.00)	10 (6.00 to 22.00)	0.248
Cr (mg/dL)	0.90 (0.48 to 13.40)	0.91 (0.58 to 13.40)	0.90 (0.48 to 1.39)	0.336

WBC = White blood cell; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase
INR = International normalize ratio; BUN = Blood urea nitrogen; Cr = Creatinine
Values are presented as n (%), mean ± SD, median (min-max), * = Significant at $p<0.05$

ribavirin therapy in the elderly with no severe comorbidities results in good treatment response. HCV viral load was another factor that was associated with treatment response in many studies in which patients with low HCV viral loads responded better to treatment than those with high ones[18,27,31]. In our study, patients with low baseline viral loads had better SVRs than those with higher loads irrespective of the treatment received, but these results were not statistically significant. Cirrhosis is associated with poor treatment response and increased risk of adverse effects from medication[19,20,32]. In the present study, SVR rates in

Table 3. Factors associated with SVR in patients with chronic hepatitis C (n = 71)

Factors	Total (n = 71)	SVR (n = 55)	No SVR (n = 16)	*p*-value
Sex				1.000
Male	51 (71.8)	39 (76.5)	12 (23.5)	
Female	20 (28.2)	16 (80.0)	4 (20.0)	
Age (year)	50.76±9.70	51.96±9.16	46.62±10.67	0.052
≤40	12 (16.9)	6 (50.0)	6 (50.0)	0.022*
>40	59 (83.1)	49 (83.1)	10 (16.9)	
BMI (kg/m^2)	23.51±3.66	23.25±3.80	24.38±3.04	0.280
<25	48 (67.6)	40 (83.3)	8 (16.7)	0.095
25 to 29.99	20 (28.2)	12 (60.0)	8 (40.0)	
≥30	3 (4.2)	3 (100.0)	0 (0.0)	
Liver Stiffness (kPa)				0.050
<12.5	33 (46.5)	29 (87.9)	4 (12.1)	
≥12.5	38 (53.5)	26 (68.4)	12 (31.6)	
Serum albumin (g/dL)	4.24±0.42	4.24±0.39	4.25±0.54	0.922
AST (U/L)	71 (23 to 225)	75 (24 to 225)	54 (23 to 161)	0.119
ALT (U/L)	85 (20 to 380)	87 (20 to 380)	46 (25 to 172)	0.006*
Platelets (cell/m^3)				0.185
≤100,000	7 (9.90)	4 (57.1)	3 (42.9)	
>100,000	64 (90.10)	51 (79.7)	13 (20.3)	
Child's pugh score				0.125
5	68 (95.8)	54 (79.4)	14 (20.6)	
6	3 (4.2)	1 (33.3)	2 (66.7)	
HCVRNA level (IU/ml)				0.163
<400,000	15 (21.1)	14 (93.3)	1 (6.7)	
≥400,000	56 (78.9)	41 (73.2)	15 (26.8)	
Type of Peginterferon				0.122
α2a	22 (31.0)	20 (90.9)	2 (9.1)	
α2b				0.019*
Treatment response at 12 weeks	49 (69.0)	35 (71.4)	14 (28.6)	
No response	18 (25.4)	10 (55.6)	8 (44.4)	
Response	53 (74.6)	45 (84.9)	8 (15.1)	
Treatment response at 24 weeks				0.011*
No response	14 (19.7)	7 (50.0)	7 (50.0)	
Response	57 (80.3)	48 (84.2)	9 (15.8)	
End of treatment response 48 weeks				0.002*
No response	14 (19.7)	6 (10.9)	8 (50.0)	
Response	57 (80.3)	49 (89.1)	8 (50.0)	
Treatment compliance				<0.001*
No complete	24 (33.8)	10 (41.7)	14 (58.3)	
Complete	47 (66.2)	45 (95.7)	2 (4.3)	
Viral genotype				0.653
Genotype 1	39 (54.9)	31 (79.5)	8 (20.5)	
Genotype 6	32 (45.1)	24 (75.0)	8 (25.0)	

BMI = Body mass index; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; SVR = Sustained virological response

Values are presented as n (%), mean ± SD, median (min-max), * = Significant at $p<0.05$

cirrhotic patients were lower than in patients without cirrhosis, but the latter group still achieved a good response rate (68.4% in cirrhosis and 87.9% in non-cirrhosis, $p = 0.050$), indicating that patients with cirrhosis without decompensation are still suitable for combination treatment with these medications. With

Table 4. Multivariate analysis for factors associated with SVR in patients with chronic hepatitis C (n = 71)

Factor	SVR	No SVR	Crude OR (95%CI)	*p*-value	Adjusted OR (95%CI)	*p*-value
Age (year)						
>40	49 (89.1)	10 (62.5)	4.90 (1.31 to 18.35)	0.018*	4.39 (0.63 to 30.77)	0.137
ALT (U/L)	87 (20 to 380)	46 (25 to 172)	1.01 (1.00 to 1.02)	0.041*	1.01 (1.00 to 1.03)	0.169
Treatment response at 12 weeks response	45 (81.8)	8 (50.0)	4.50 (1.36 to 14.88)	0.014*	3.96 (0.20 to 79.62)	0.369
Treatment response at 24 weeks response	48 (87.3)	9 (56.2)	5.33 (1.50 to 18.93)	0.010*	0.41 (0.02 to 8.27)	0.561
End of treatment response 48 weeks response	49 (89.1)	8 (50.0)	8.17 (2.24 to 29.84)	0.001*	2.55 (0.43 to 15.11)	0.303
Treatment compliance complete	45 (81.8)	2 (12.5)	31.50 (6.16 to 161.15)	<0.001*	18.14 (2.72 to 121.01)	0.003*

ALT = Alanine aminotransferase; SVR = Sustained virological response , OR = Odds ratio; CI = Confidence interval
Values are presented as n (%), median (min-max), * = Significant at $p<0.05$

regard to type of peginterferon for treatment of CHC and its effects on treatment response, a recent meta-analysis and systematic review showed that peginterferon alfa 2a was more effective than peginterferon alfa 2b[33,34]. These findings were in agreement with the findings of the present study, but no statistical significance was observed (90.9% with peginterferon alfa 2a and 71.4% with peginterferon alfa 2b, $p = 0.122$).

In multivariate analysis, the only factor associated with SVR was treatment compliance with the 80/80/80 rule (95.7% and 41.7% in compliant and non-compliant patients respectively, $p = 0.004$), and this finding was consistent with results of previous studies[35,36]. The main problems of treatment compliance are long duration of treatment in CHC genotypes 1 and 6, and adverse events from medication. Because of the high treatment response success rates in patients with good adherence to treatment, limitations in the availability of DAAs, and budget constrictions, combinations of peginterferon and ribavirin are still suitable regimens for CHC in Thailand.

The limitations of this study were its small sample size, and the heterogeneity of type of peginterferon alfa and ribavirin doses. Therefore, larger numbers of subjects in a prospective study are needed to confirm the results of the present research.

Conclusion

Combinations of treatment with peginterferon alfa plus ribavirin for 48 weeks are still effective for treatment of CHC genotypes 1 and 6. Selection of suitable patients and good treatment compliance are important factors for achieving SVR.

What is already known on this topic?

Chronic hepatitis C patients with genotypes 1 and 6 are very prevalent in Thailand and have a major impact on public health. Treatment with peginterferon plus ribavirin has drawbacks in terms of its moderate efficacy, long duration of treatment and adverse side effects.

Sustained virological response rates 24 weeks after end of treatment (SVR) for patients with genotypes 1 and 6 hepatitis C infection are about 42 to 52% and 60 to 90% respectively and less impressive than SVR patients with genotype 3 hepatitis C infection.

What this study adds?

Response rates of CHC genotypes 1 and 6 to treatment with peginterferon alfa plus ribavirin were

better than average response rates and consistent with other studies from Asian countries.

Selection of suitable patients and good treatment compliance resulted in high SVR rates comparable to treatment with DAA regimens .

Acknowledgements

This research was supported by a research grant from Rajavithi Hospital. The authors would like to thank to all Gastrointestinal (GI) staff, Gastrointestinal (GI) fellows and hepatology nurses at the GI clinic, Division of Gastroenterology, Department of Medicine, Rajavithi Hospital. The authors would also like to acknowledge the assistance of staff of the Department of Tropical Medicine for statistical and data analysis advice, and would also like to express their appreciation to the staff of the Division of Medical Research, Department of Research and Technology Assessment, Rajavithi Hospital, for data analysis and research paper preparation.

Potential conflicts of interest

None.

Reference

1. Tong MJ, el-Farra NS, Reikes AR, Co RL. Clinical outcomes after transfusion-associated hepatitis C. N Engl J Med 1995; 332: 1463-6.
2. Zarski JP, Mc Hutchison J, Bronowicki JP, Sturm N, Garcia-Kennedy R, Hodaj E, et al. Rate of natural disease progression in patients with chronic hepatitis C. J Hepatol 2003; 38: 307-14.
3. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology 2008; 48: 418-31.
4. Grebely J, Page K, Sacks-Davis R, van der Loeff MS, Rice TM, Bruneau J, et al. The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection. Hepatology 2014; 59: 109-20.
5. Global surveillance and control of hepatitis C. Report of a WHO Consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium. J Viral Hepat 1999; 6: 35-47.
6. World Health Organization. Hepatitis C[internet]. 2017 [cited 2017 july 10]. Available from: http://www.who.int.mediacentre/factsheets/ fs164/en.
7. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol 2014; 61 (1 Suppl): S45-57.
8. Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol 2017; 2: 161-176.
9. Cavalcante LN, Lyra AC. Predictive factors associated with hepatitis C antiviral therapy response. World J Hepatol 2015; 7: 1617-31.
10. 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: 126764.
11. Omata M, Kanda T, Wei L, Yu ML, Chuang WL, Ibrahim A, et al. APASL consensus statements and recommendation on treatment of hepatitis C. Hepatol Int 2016; 10: 702-26.
12. AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology 2015; 62: 932-54.
13. Thai Association for the Study of the Liver. Thailand Practice Guideline for Management of Chronic Hepatitis C. Bangkok: parbpim; 2016
14. European Association for Study of Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol. 2014; 60: 392-420.
15. Swain MG, Lai MY, Shiffman ML, Cooksley WG, Zeuzem S, Dieterich DT, et al. A sustained virological response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. Gastroenterology. 2010; 139: 1593-601.
16. Morgan TR, Ghany MG, Kim HY, Snow KK, Shiffman ML, De Santo JL, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology 2010; 52: 833-44.
17. Hauser G, Awad T, Thorlund K, Stimac D, Mabrouk M, Gluud C. Peginterferon alpha-2a versus peginterferon alpha-2b for chronic hepatitis C. Cochrane Database Syst Rev 2014 28; CD005642.
18. Nguyen LH, Nguyen MH. Systematic review: Asian patients with chronic hepatitis C infection. Aliment Pharmacol Ther. 2013; 37: 921-36.
19. 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.
20. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL Jr, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002; 347: 975-82.
21. Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, et al. Peginterferon-alpha 2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004; 140: 346-55.
22. Nguyen MH, Trinh HN, Garcia R, Nguyen G, Lam KD, Keeffe EB. Higher rate of sustained virologic response in chronic hepatitis C genotype 6 treated with 48 weeks versus 24 weeks of peginterferon plus ribavirin. Am J Gastroenterol 2008; 103: 1131-5.
23. Kemp W, Levy M, Weltman M, Lubel J; Australian Liver Association (ALA). Australian Liver Association (ALA) expert consensus recommendations for the use of transient elastography in chronic viral hepatitis. J Gastroenterol Hepatol 2015; 30: 453-62.
24. Nguyen NH, VuTien P, Garcia RT, Trinh H, Nguyen H, Nguyen K, et al. Response to pegylated interferon and ribavirin in Asian American patients with chronic hepatitis C genotypes 1 vs 2/3 vs 6. J Viral Hepat 2010; 17: 691-7.
25. Tsang OT, Zee JS, Chan JM, Li RS, Kan YM, Li FT, et al. Chronic hepatitis C genotype 6 responds better to pegylated interferon and ribavirin combination therapy than genotype 1. J Gastroenterol Hepatol 2010; 25: 766-71.
26. Chuang WL, Yu ML. Host factors determining the efficacy of hepatitis C treatment. J Gastroenterol 2013; 48: 22-30.
27. Roeder C, Jordan S, Schulze Zur Wiesch J, Pfeiffer-Vornkahl H, Hueppe D, Mauss S, et al. Age-related differences in response to peginterferon alfa-2a/ribavirin in patients with chronic hepatitis C infection. World J Gastroenterol 2014; 20: 10984-93.
28. Frei P, Leucht AK, Held U, Kofmehl R, Manser CN, Schmitt J, et al. Elderly age is not a negative predictive factor for virological response to therapy with pegylated interferon-alpha and ribavirin in chronic hepatitis C virus patients. Liver Int 2014; 34: 551-7.
29. Nishikawa H, Iguchi E, Koshikawa Y, Ako S, Inuzuka T, Takeda H, et al. The effect of pegylated interferon-alpha2b and ribavirin combination therapy for chronic hepatitis C infection in elderly patients. BMC Res Notes 2012; 5: 135.
30. Yu ML1, Chuang WL. Treatment of chronic hepatitis C in Asia: when East meets West. J Gastroenterol Hepatol 2009; 24: 336-45.
31. Horoldt B, Haydon G, O'Donnell K, Dudley T, Nightingale P, Mutimer D. Results of combination treatment with pegylated interferon and ribavirin in cirrhotic patients with hepatitis C infection. Liver Int 2006; 26: 650-9.
32. Flori N, Funakoshi N, Duny Y, Valats JC, Bismuth M, Christophorou D, et al. Pegylated interferon-alpha2a and ribavirin versus pegylatedinterferon-alpha2b and ribavirin in chronic hepatitis C: a meta-analysis. Drugs 2013; 73: 263-77.
33. McHutchison JG, Manns M, Patel K, Poynard T, Lindsay KL, Trepo C, et al. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. Gastroenterology 2002; 123: 1061-9.
34. Manns MP, Wedemeyer H, Cornberg M. Treating viral hepatitis C: efficacy, side effects, and complications. Gut 2006; 55: 1350-9.