Effectiveness of Anti-Viral Medications for Treatment of Chronic Hepatitis C: A Retrospective Study in a Tertiary Care Hospital in Northeast Thailand

Bupachart Nunthaithaweekul* Tepsun Seearamroongruang** Manoon Mitpracha**
Pornanan Domthong** Kittiya Piyasin*** Wilasinee Kamonmit*** Pissana Khonhome***
Guntaragorn Hongrattana**** Acharawan Topark-ngarm[1]*****

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ABSTRACT

The objectives of the study were to assess the effectiveness of the anti-viral medications for treatment of chronic hepatitis C virus (HCV) infection and the factors associated with the effectiveness. The method was a retrospective study conducted in outpatients treated with anti-HCV medications at Khon Kaen hospital during January 1st 2019 to December 31st 2020. Demographic, social history, and medical history data were collected from medical records. Effectiveness was determined as an undetectable HCV RNA in the blood (<25 IU/mL) at 12 weeks post-treatment (Sustained Virologic Response; SVR12) and analyzed using descriptive analysis. Multivariate logistic regression analysis was used to identify factors associated with the effectiveness. The results showed that from a total of 160 patients included to the study, HCV genotypes 1, 3, 6 were found in 38.8, 43.1, and 18.1%, respectively. Majority of the patients were male (76.2%) and the average age was 50.5years. There were 75 patients (46.9%) having cirrhosis, 16 (10.0%) having HIV infection, and 22 (13.8%) having a previous treatment failure. Overall, SVR12 was achieved in 153 patients (95.6%). The SVR12 rate of genotype 3 was 98.6%. Patients with HCV genotype 1 achieved SVR12 at 95.7% in non-cirrhosis group and 94.9% in cirrhosis group. Similarly, SVR12 of genotype 6 patients was achieved in 100% and 84.2% in non-cirrhosis and cirrhosis group, respectively. Three significant factors, including female gender (adjusted odds ratio (OR) 0.11; 95% CI 0.02-0.85), co-infection with HIV (OR 0.06; 95% CI 0.01-0.53) and genotype 6 with cirrhosis (OR 0.04; 95% CI 0.01-0.45), were negatively associated with treatment effectiveness. In conclusions, anti-HCV treatment was effective for genotype 1, 3, and 6 infections. The patients with no cirrhosis were likely to have better respond to the anti-HCV treatment. Female gender, co-infection with HIV, and genotype 6 with cirrhosis were significant factors negatively affecting effectiveness of HCV treatment.

Keywords: Hepatitis C virus infection, anti-viral medications, Sustained Virologic Response

[1]*Corresponding author: achkha@kku.ac.th*

**Student, Master of Pharmacy Program in Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Khon Kaen University, Thailand*

***Physician, Khon Kaen Hospital, Khon Kaen, Thailand*

****Pharmacist, Khon Kaen Hospital, Khon Kaen, Thailand*

*****Statistician, Khon Kaen Hospital, Khon Kaen, Thailand*

******Assistant Professor, Division of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Khon Kaen University, Thailand*

Introduction

The Hepatitis C Virus (HCV) infection can lead to cirrhosis, liver failure and hepatocellular carcinoma [1]. Most of HCV infected patients have no clinical symptoms and that would made them unaware of the infection until reaching to a terminal stage of the disease. Without proper treatment, the disease can progress from infection to liver insufficiency, cirrhosis and liver cancer. Usually, liver cancer occurs after 20-30 years of infection [2]. The American Liver Foundation notes that around 15-20% of people who have acute HCV will recover without treatment. However, approximately 75-85% will develop chronic HCV infection [3]. The World Health Organization currently estimates the global burden of Hepatitis C to be between 130 and 170 million people, 30 million people being carriers and HCV causing death is approximately 120,000 cases per year [1]. In Thailand, HCV infection has been reported with a prevalence of 2.2%, with the highest number found in Northern and North-Eastern areas. The most common genotype types of HCV found are 1, 2, 3 and 6 [4-5].

The aim of HCV treatment is to eradicate the HCV which can improve pathologic changes of liver, prevent complications and disease progression by achieving Sustained Virologic Response (SVR) or undetectable plasma HCV RNA using a highly sensitive PCR assay at 12 weeks after completion of the treatment (SVR12) [6]. In most cases, having SVR means a person's liver will no longer become damaged by HCV [6].

Triple drug combination of peg-interferon, ribavirin and New Oral Direct-acting Antivirals (DAAs) has been reported to achieve SVR12 greater than 95%. However, success rate of treatment has been found to be different among races which could be explained by a differ in HCV strains (genotype) and genetic backgrounds [7-8].

It has been reported that many factors are associated with treatment success. It has been shown that the incidence of effectiveness among patients with HIV co-morbid is lower than in those without HIV co-morbid. Besides, the patients who were naïve to the treatment seem to have less treatment failure than those who were non-naïve [9].

New Oral Direct-acting Antivirals such as sofosbuvir, sofosbuvir/ ledipasvir, daclatasvir, elbasvir/grazoprevir, sofosbuvir/velpatasvir, boceprevir, and telaprevir have been recently available and clinically proved with very high efficacy, tolerable side effects and ease of use [10]. In Thailand, DAAs have been available with more accessible price and that made their journey now being enlisted in the Thailand National List of Essential Medicine (NLEM). Sofosbuvir, sofosbuvir/ledipasvir, peg-interferon, and ribavirin are now under coverage of Social Security, Universal Health Coverage, and Civil Servant Service schemes [11]. The 2018 Thailand management guidelines of HCV recommends standard drugs, sofosbuvir and ledipasvir, in treatment of non-cirrhotic patients infected with HCV genotype 1, 2, 4, and 6. In case of cirrhosis, ribavirin is recommended to add on the treatment regimen of sofosbuvir and ledipasvir [11]. For genotype 3, the guideline recommends sofosbuvir, peg-interferon alfa and ribavirin for both cirrhotic and non-cirrhotic patients [11].

The treatment of HCV infection has been implemented country-wide in Thailand under the health insurance coverage and reimbursement since 2018. To our knowledge, little data is available regarding effectiveness of the treatment in the real settings. Published evidence from clinical trials cannot guarantee the outcomes actually happens in real situations. Therefore, knowledge on drug response in real settings will be asset for health care professional in planning for optimal care. Thus, this study was conducted and aimed to determine the response to new therapeutic approaches of HCV in Khon Kaen Hospital, a public tertiary care hospital which having referred patients from district hospitals in Khon Kaen province and neighboring provinces in Northeast of Thailand.

Objective of the Study

This study was aimed to determine the effectiveness of HCV treatment and factor associated with the effectiveness in Khon Kaen Hospital, a public tertiary care hospital in northeast of Thailand.

Methodology

This study was a retrospective study conducted by medical chart review. Patients who were diagnosed with chronic HCV infection and treated with anti-HCV drugs at Khon Kaen Hospital as outpatients between January 1, 2019 and December 31, 2020 were enrolled in the study.

Inclusion criteria: Patients who were diagnosed with chronic HCV infection with the ICD-10 code B182, age of 18 or older, had a level of HCV RNA greater than 5,000 IU/mL before starting the treatment, had GFR greater than 30 mL/min/1.73 m^2 and received anti-HCV drugs.

Exclusion criteria: Patients who their medical records could not be accessed or lacked critical data for analysis, referred to other hospitals, unable to be followed up during the treatment, did not complete the treatment due to death, having drug intolerability or toxicity, refused to continue the treatment or having poor compliance.

Sample size calculation: The sample size in this study was determined by the response rate which was defined as undetectable HCV RNA (<25 IU/ml) 12 weeks after completion of the treatment. The sample size was calculated according to a formula that actual number of populations is unknown [12], as follows:

$$n = (Z\alpha_{/2})^2 * p(1-p) / d^2$$

$Z\alpha_{/2}$= confidence interval , P = proportion, d = Precision level

1. The response rate of chronic HCV treatment for genotype 1, 2, 4, 6 with Sofosbuvir/Ledipasvir plus Ribavirin (SOF/LDV+RBV) group was set as 0.96 (p = 0.96) [13] with $Z_{0.05}$, Confidence level = 1.96 and Precision level (d) = 0.05. The sample size was calculated as follows:

$$n = (Z\alpha_{/2})^2 * p(1-p) / d^2$$
$$= [(1.96)^2*0.96(1-0.96)] / [0.05]^2] = 59.0$$

2. The response rate of chronic HCV treatment for genotype 3 with Sofosbuvir + Peg-interferon alfa + Ribavirin (SOF + Peg-IFN + RBV) group was set as 0.90 (p = 0.90) [14] with $Z_{0.05}$, Confidence level = 1.96 and Precision level (d) = 0.07. The sample size was calculated as follows:

$$n = (Z\alpha_{/2})^2 * p(1-p) / d^2$$
$$= [(1.96)^2*0.90(1-0.90)] / [0.07]^2 = 70.56$$

Based on the calculation above, a sample size of patients treated with Sofosbuvir/Ledipasvir + Ribavirin (SOF/LDV + RBV) for chronic HCV genotypes 1, 2, 4, and 6 is 59 and treated with Sofosbuvir+ Peg-interferon alfa + Ribavirin (SOF + Peg-IFN + RBV) for genotype 3) was 71. The researcher therefore added the number of sample size by 20%, compensating for a typical portion of lost to follow up. A number of sample size used in this study was as follows:

$$(59+71) \times 1.2 = 156$$

Therefore, this study collected data on 160 patients who received treatment for chronic HCV infection genotypes 1, 2, 3, 4, and 6.

Data Collection

Data was collected from a computerized hospital outpatient database and medical records. Study variables included age, gender, weight, height, alcoholic consumption, cirrhosis, co-infection with HIV, comorbidities, HCV genotype, baseline HCV viral load, history of previous HCV treatment and the current HCV treatment, and blood HCV RNA at 12 weeks post-treatment.

Data Analysis

Demographic data and patient characteristics, including gender, age range, weight, history of alcoholic consumption, history of cirrhosis, co-infection with HIV, comorbidities, HCV genotype, baseline HCV viral load, history of previous treatment and current treatment, was analyzed using descriptive statistic. Data was shown as frequency, percentage, mean (s.d.), or median (interquartile 25,75). Effectiveness of treatment was defined as undetectable HCV RNA (<25 IU/mL) in blood at 12 weeks post-treatment (SVR12) and presented as percentage of patient achievement classified by genotype. Factors associated with effectiveness were analyzed using bivariate analysis. Then all the variables with p <0.25 were subsequently tested statistically with multivariate logistic regression. Statistical significance was considered when p<0.05. The STATA program version 14 was used for statistical analysis.

Research ethics

This research was approved by the Khon Kaen University Ethics Committee for Human Research (Project No. HE642183) and by the Khon Kaen Hospital Office of the Human Research Ethics Committee (Project No. KEMOU64025).

Results

In this study, 160 patients met the inclusion and exclusion criteria and the sample size requirement. Among these, 122 patients were male (76.2%). The median BMI was 24 and the average age was 50.5. Only 11 patients (6.9%) had a history of alcohol consumption. Among 106 patients (66.3%) who had one or more comorbidities, the common ones were alcoholic cirrhosis (75 patients; 46.9%) and co-infection with HIV (16 patients, 10.0%). The median HCV viral load was approximately 1,300,000 IU/mL. The most common prevalent genotype found in this study was genotype 3 (69 patients, 43.1%), followed by genotype 1 (62 patients, 38.8%) and genotype 6 (29 patients, 18.1%). Infection with genotype 2, 4, and 5 was not found in this study. Failure to a previous treatment was found in 22 patients (13.8%). The rates of responder and non-responder classified by individual characteristic are demonstrated in Table 1.

Effectiveness of Chronic Hepatitis C Antiviral Drugs

This study found that 153 patients had a sustained virologic response (SVR12), accounting for the overall response rate of 95.6% as shown in **Table 1.** In genotype 3 group, which were treated with sofosbuvir, peg-interferon alfa and ribavirin, 68 out of 69 (98.6%) achieved SVR12. Among 62 patients with genotype 1 infection, 23 of these had no cirrhosis and treated with sofosbuvir and ledipasvir for 12 weeks, while the other 39 patients who had cirrhosis were treated with sofosbuvir and ledipasvir plus ribavirin for 12 weeks. The SVR12 of these two groups were 95.7% (22 out of 23) and 94.9% (37 out of 39), respectively. In a group of 29 patients with genotype 6, 10 of these had no cirrhosis and treated with sofosbuvir and ledipasvir for 12 weeks, while 19 had cirrhosis and treated with sofosbuvir and ledipasvir plus ribavirin for 12 weeks. SVR12 was achieved in 10 out of 10 (100%) in no-cirrhosis group and 16 out of 19 (84.2%) in the cirrhosis group. The SVR12 classified by genotype are shown in Figure 1.

Factors Associated with the Effectiveness of Chronic Hepatitis C Antiviral Drugs

Bivariate analysis was used to analyze factors associated with the effectiveness of anti-HCV drugs. This study compared the variables between two groups, those who did (n=153) and did not (n=7) achieved SVR12 as shown in Table 2. Female gender, age, BMI, alcohol consumption, cirrhosis, co-infection with HIV, history of treatment failure, HCV RNA viral load before treatment, comorbidity, and

HCV genotype, were variables used for comparison between responder and non-responder groups. The results showed that co-infection with HIV (OR 0.12, 95% CI 0.02-0.61, p = 0.01) and genotype 6 with cirrhosis (treated with ribavirin-containing regimen, OR 0.15, 95% CI 0.03-0.75, p = 0.02) were significant prognostic factors associated with effectiveness. In fact, the response rate of a group with no HIV co-infection was 140 out of 144 (97.2%) and a group with HIV infection was 81.3%. For genotype 6, the response rate between non-cirrhosis and cirrhosis groups was 100% vs. 84.2%, respectively. Age and genotype 6 with no cirrhosis were the variables that could not be ruled out whether they were factor associated with effectiveness (Table 2).

Multivariate logistic regression analysis was subsequently performed on factors that had significant values (p-value) of 0.25 or less, including female gender, cirrhosis, co-infection with HIV, history of treatment failure, HCV-RNA viral load before treatment <2,100,000, >1 comorbidity, genotype 3, and genotype 6 with cirrhosis (ribavirin treatment group). The results showed three significant factors were associated with effectiveness of the treatment. In addition to two factors, HIV co-infection and genotype 6 with cirrhosis, female was another factor associated with effectiveness. In fact, a response rate of female group was 89.5% (34 out of 38 patients), compared to male group that was 97.5% (119 out of 122 patients). All adjusted OR values of these variables were shown in Table 2.

Discussion and Conclusions

From this research, the effectiveness of chronic hepatitis C antiviral drugs, recommended by the Thailand HCV Treatment Practice Guideline 2018, were evaluated in the real setting. In this research, overall responsive rate was 95.6%. The three variables negatively affecting the effectiveness of antiviral treatments for chronic hepatitis C were identified, including genotype 6 with cirrhosis, co-infection with HIV, and female gender.

Cirrhosis has been reported to be a factor correlated with non-responsiveness in several studies [15-16]. A previous systematic review found that SVR12 achievement rate of the patients with cirrhosis was 91.3%, significantly lower than patients without cirrhosis (97.7%) [15]. Moderate and severe cirrhosis groups have been reported with SVR12 rates of 85-88% and 60-75%, compared to 96-98% in a group without cirrhosis [16]. In this study, the response rate or achievement of SVR12 was found higher in no cirrhosis than cirrhosis group (83 out of 85; 97.6% vs. 70 out of 75; 93.3%). When considering for a specific genotype, genotype 1 patients with no cirrhosis achieved SVR12 at 95.7% compared to 94.9% in cirrhosis patients. For genotype 6, the SVR12 between non-cirrhosis and cirrhosis groups was 100% vs. 84.2%, respectively. In fact, by multivariate analysis, this study showed that having genotype 6 infection with cirrhosis was a factor significantly associated with non-response to the treatment. This may be explained that cirrhosis together with a nature of genotype 6 infection are likely to have a combined effect on response of the treatment.

Co-infection with HIV and gender were shown in this study as factors related to non-responsive by multi-variate analysis. In fact, the response rate of a group with no HIV co-infection was 140 out of 144 (97.2%) and that of a group with HIV infection was 13 out of 16 (81.3%). These findings were consistent with the studies of Milazzo et al [17]. A response rate of female group in this study was 89.5% (34 out of 38 patients), compared to male group that was 97.5% (119 out of 122 patients). The study reported by Kanwal et al consistently showed that female has a strong influence on treatment failure [7].

With a nature of retrospective study, there were limitations of data collection. According to the regulations for treating chronic hepatitis C in 2019–2020 by the National Health Security Office (NHSO), all medications for the whole 12-week treatment period were now allowed to provide to the patients at once. The patients were required to have 3 rounds of hospital visits for follow-up and receiving the next round of medications. For some patients, this caused inconvenience, and then missed their hospital appointments. To determine the responsiveness in a real-world situation, this study enrolled only those who had good compliance with the treatment, did not miss any follow-up schedules, and those who had no serious ADRs that led to discontinuation of treatment or switching to other drugs. As a result, this may explain high response rate to the treatment reported in this study. Further studies are required to determine the responsiveness in non-compliance group and safety of anti-HCV drugs.

This study illustrated that the anti-HCV drugs recommended by the Thailand HCV Treatment Practice Guideline 2018 were effective. The findings also shade a light on factors negatively affecting effectiveness of HCV treatment. These can benefit health care professionals in their planning for treatment. In particular, patients with HIV, infected with genotype 6, and having cirrhosis that should be monitored closely as they may have higher risks of treatment failure and need different approach of care.

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Table 1 Demographic data

Variables	Total (N=160)		Total (N=160)
	Responder (N=153) N (%)	Non-responder (N=7) N (%)	
Gender			
Male	119 (77.8)	3 (42.8)	122 (76.2)
Female	34 (22.2)	4 (57.1)	38 (23.8)
Age (year), mean (SD)			50.5 (8.3)
≥60	21 (13.7)	0 (0)	21 (13.1)
<60	132 (86.3)	7 (100)	139 (86.9)
BMI (kg/m^2), median (IQR)			24 (22.4, 26.4)
≥25	54 (35.3)	2 (28.6)	56 (35.0)
<25	99 (64.7)	5 (71.4)	104(65.0)
Alcohol consumption			
Yes	10 (6.5)	1 (14.3)	11 (6.9)
No	143 (93.5)	6 (85.7)	149 (93.1)
Cirrhosis			
Yes	70 (45.8)	5 (71.4)	75 (46.9)
No	83 (54.2)	2 (28.6)	85 (53.1)
Co-infection with HIV			
Yes	13 (8.5)	3 (42.8)	16 (10.0)
No	140 (91.5)	4 (57.1)	144 (90.0)
History of treatment failure			
Yes	20 (13.1)	2 (28.6)	22 (13.8)
No	133 (86.9)	5(71.4)	138(86.2)
HCV-RNA viral load, median (IQR) IU/ml			1,365,543 (211,510 , 4,864,488)
<2,100,000	90 (58.8)	2 (28.6)	92 (57.5)
≥2,100,000	63 (41.2)	5 (71.4)	68 (42.5)
Comorbidity			
Yes	100 (65.3)	6 (85.7)	106 (66.3)
No	53 (34.6)	1 (14.2)	54 (33.7)
Number of comorbidities			
>1	59 (38.5)	5 (71.4)	64 (40.0)
≤1	94 (61.4)	2 (28.6)	96 (60.0)
Genotype and treatment regimen			
Genotype 1			62 (38.8)
- Sofosbuvir and Ledipasvir (no cirrhosis)	22 (14.4)	1 (14.3)	23 (14.4)
- Sofosbuvir and Ledipasvir plus Ribavirin (cirrhosis)	37 (24.2)	2 (28.6%)	39 (24.4)
Genotype 3 (Peg-IFN, Sofosbuvir, plus Ribavirin)	68 (44.4)	1 (14.3%)	69 (43.1)
Genotype 6			29 (18.1)
- Sofosbuvir and Ledipasvir (no cirrhosis)	10 (6.5)	0 (0)	10 (6.2)
- Sofosbuvir and Ledipasvir plus Ribavirin (cirrhosis)	16 (10.5)	3 (42.8)	19 (11.9)

Table 2 Factor Related to Effectiveness of Anti-HCV Treatment

Variables	Crude OR	95% CI	*p*-value	Adjusted OR	95% CI	*p*-value
Female	0.21	0.05 to 1.00	0.05	0.11	0.02 to 0.85	0.03
Age ≥60	-	-	-	-	-	-
Body mass index ≥25	1.36	0.26 to 7.27	0.72	-	-	-
Alcohol consumption, yes	0.42	0.46 to 3.83	0.44	-	-	-
Cirrhosis, yes	0.34	0.06 to 1.79	0.20	0.26	0.05 to 2.01	0.23
Co-infection with HIV, yes	0.12	0.02 to 0.61	0.01	0.06	0.01 to 0.53	0.01
History of treatment failure, yes	0.38	0.07 to 2.07	0.25	0.13	0.01 to 1.30	0.08
HCV-RNA viral load <2,100,000	3.57	0.67 to18.91	0.13	3.14	0.27 to 4.03	0.25
Comorbidity, yes	0.31	0.04 to 2.68	0.29	-	-	-
Comorbidities >1	0.25	0.05 to 1.34	0.11	3.58	0.25 to 4.59	0.26
Genotype						
Genotype 1 with no cirrhosis (Sofosbuvir and Ledipasvir)	1.01	0.12 to 8.77	0.99	-	-	-
Genotype 1 with cirrhosis (Sofosbuvir and Ledipasvir plus Ribavirin)	0.79	0.14 to 4.28	0.79	-	-	-
Genotype 3	4.79	0.56 to 4.83	0.15	3.63	0.32 to 4.95	0.29
Genotype 6 with no cirrhosis (Sofosbuvir and Ledipasvir)	-	-	-	-	-	-
Genotype 6 with cirrhosis (Sofosbuvir and Ledipasvir plus Ribavirin)	0.15	0.03 to 0.75	0.02	0.04	0.01 to 0.45	0.01

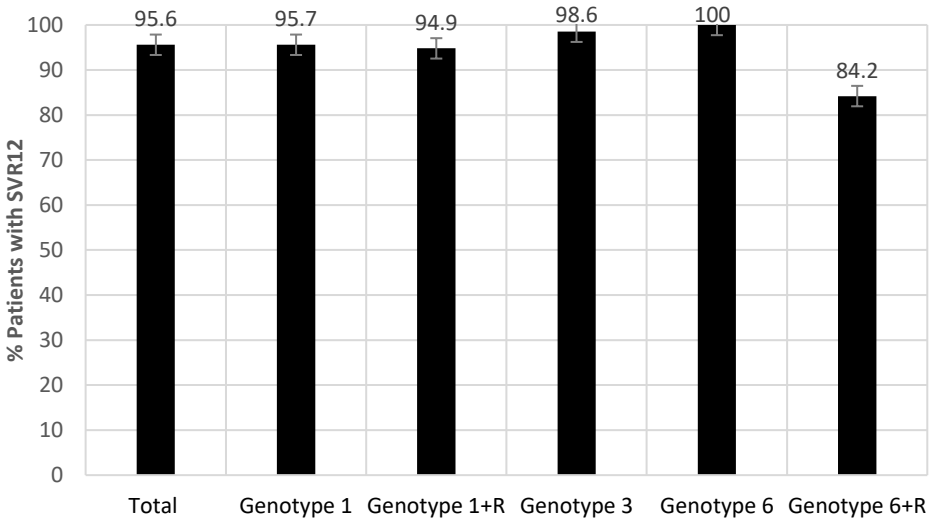

Figure 1 Effectiveness of the Anti-HCV Drugs Classified by Genotype; **(1)** Total: 153/160, **(2)** Genotype 1 (with no cirrhosis, treated with Sofosbuvir and Ledipasvir): 22/23, **(3)** Genotype1+R (with cirrhosis, treated with Sofosbuvir and Ledipasvir plus Ribavirin): 37/39, **(4)** Genotype 3: 68/69, **(5)** Genotype 6 (with no cirrhosis, treated with Sofosbuvir and Ledipasvir): 10/10, **(6)** Genotype 6+R (with cirrhosis, treated with Sofosbuvir and Ledipasvir plus Ribavirin): 16/19.