ASSESSMENT THE RESULTS OF SOFOSBUVIR/VELPATASVIR TREATMENT IN CHRONIC HCV - INFECTED PATIENTS AT NATIONAL HOSPITAL FOR TROPICAL DISEASES

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Summary

Objectives: To evaluate the results of treatment of patients with chronic hepatitis C with Sofosbuvir/Velpatasvir regimen and adverse effects of the regimen. *Subjects and methods:* A cross sectional descriptive study with follow up 12 weeks after the end of treatment. 46 patients confirmed diagnosis of chronic hepatitis C according to 2016 Guidelines for diagnosis and treatment of hepatitis C virus of Ministry of Health. They received Sofosbuvir 400mg/Velpatasvir 100mg combination once daily for 12 weeks. Patients were followed up six months after the start of therapy. Hepatitis C viral load was assessed at baseline, at week 4 and after 24 weeks following the start of the treatment. *Result:* 34 patients without cirrhosis (97.1%) and 10 patients with compensated cirrhosis (90.9%) achieved RVR. A total of 100% of patients without cirrhosis and 90.9% of patients with compensated cirrhosis achieved SVR 12 weeks after the end of therapy. Patients with compensated cirrhosis experienced more adverses events (45.5%) than patients without cirrhosis (8.57%). None of the patients without cirrhosis or with compensated cirrhosis experienced any serious adverse event. A few patients complained about some symtoms such as fatigue (6/46, 13.0%), ichy/rash (2/46, 4.3%), insomnia (2/46, 4.3%), jaundice (1/46, 2.1%) - which appeared after received Sofosbuvir/Velpatasvir therapy. Most certain laboratoty abnormalities were seen in patients with compensated cirrhosis. *Conclusion:* The therapy of sofusbuvir/velpatasvir combination daily for 12 weeks is safe and efficacious in hepatitis C patients without cirrhosis or with compensated cirrhosis, irrespective of the genotype.

Key words: Hepatistis C, treatment effectiveness, sofosbuvir, velpatasvir, sustained virologic response.

INTRODUCTION

Hepatitis C virus is one of the main cause of chronic liver disease[1]. HCV becomes a main concern health issue on over the world with an incidence rate of 2.8%, equivalent to more than 185 million people with hepatitis C worldwide and about 35,000 deaths each year[2]. Without treatment, HCV can lead to cirrhosis, liver cancer and possibly death. In Vietnam, the proportion of anti - HCV carriers accounts for about 1 - 6% of the population, but this rate varies depending on each risk group[3].

The introduction of direct antiviral drugs (DAAs) in 2011 made a great opportunity in the treatment of chronic hepatitis C. Direct antivirals are safe, have few side effects, are well tolerated and shorten treatment time with prolonged SVR. The fixed dose combination regimen Sofosbuvir 400mg/Velpatasvir 100mg is one of the DAAs drugs currently recommended for using in the chronic hepatitis C treatment guidelines[4]. Sofosbuvir belongs to the class of NS5B RNA polymerase inhibitors, while Velpatasvir belongs to the group of inhibiting NS5A proteins

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of hepatitis C virus[5]. The combination regimen of Sofosbuvir 400mg/Velpatasvir 100mg is recommended for patients with chronic hepatitis C without cirrhosis or with compensated cirrhosis, 1 tablet daily for 12 weeks. The advantages of this regimen are not only highly effective in treating new patients, but also could be used for all six hepatitis C virus genotypes. In addition, the safety of the combination of Sofosbuvir and Velpatasvir in the treatment of chronic hepatitis C has also been demonstrated with a low rate of undesirable effects[6].

Vietnam is located in the endemic zone of hepatitis C virus with a high rate. Sofosbuvir/Velpatasvir is also recommended by Ministry of Health in 2016. However, there has been no research for evaluating the therapeutic efficacy and safety of the fixed - dose combination regimen Sofosbuvir 400mg/Velpatasvir 100mg in patients with chronic hepatitis C virus infection. We conducted this study to evaluate the results of treatment of patients with chronic hepatitis C with Sofosbuvir/Velpatasvir regimen and adverse effects of the regimen.

MATERIALS AND METHODS

Study Design: A cross sectional descriptive study with follow up 12 weeks after the end of treatment.

Setting and participants: Fourty six patients confirmed diagnosis of chronic hepatitis C in Outpatient Department of National hospital for tropical diseases were enrolled in the study. All patients were enrolled using a convenient sampling procedure. The study duration was from February 2018 to February 2020.

Selection criteria: Age ≥ 18 years old; Diagnosis chronic hepatitis C infection according to 2016 Guidelines for diagnosis and treatment of hepatitis C virus[4]; Patient has not been treated with hepatitis C antivirals.

Patient was treated with Sofosbuvir 400mg/Velpatasvir 100mg at 1 tablet/day for 12 weeks.

Exclusion criteria:

- Co - infected with other hepatitis viruses such as HBV, HEV, HAV…
- HIV co - infected patient.
- Patients with decompensated cirrhosis, liver cancer.
- Patients with surgical diseases causing gastrointestinal disturbances affecting the absorption of drug.
- Patients on long term use of systemic immunosuppressants.
- Pregnant and lactating women.
- Patients who did not take test at the time according to guidelines for diagnosis and treatment of hepatitis C of Vietnam Ministry of Health.

Outcomes: HCV viral load by COBAS AmpliPrep/COBAS TaqMan48 - ROCHE with a detection limit of < 15IU/mL was obtained at week 4 and week 24. The primary endpoint was the achievement of SVR. An SVR was defined as an undetectable viral load at 24 weeks from the start of therapy. An RVR was defined as an undetectable viral load at 4 weeks from the start of therapy.

Statistical analysis: All data were entered and analyzed on STATA 11.0. Frequencies and percentages were measured for the qualitative variables. Mean and standard deviations were reported for quantitative data. Data for non-standard distribution variables will be expressed as median and quartile interval (IQR). Our study used the Student test for continuous variables with normal distribution and Wilcoxon for non - standard distribution. For continuous variables with non - standard distribution, we use the Kruskal Wallis test. The difference is considered statistically significant when $p < 0,05$.

Limitation of the study: The number of patients in this study is small and the follow - up time is only 12 weeks after the end of treatment, so the result has not shown all the changes in liver fibrosis level and the study has not yet evaluated the rate of SVR24.

RESULTS AND DISCUSSION

Among the 64 enrolled patients, 69.6% were male and 30.4% were female. Among them, 35 (76.1%) were without cirrhosis and 11 (23.9%) had compensated cirrhosis. The mean age of patients in this study is 47.6 ± 22.3 years. Most of the patients were infected with genotype 6 (21, 45.7%) or genotype 1 (14, 30.4%); a minority were infected with genotype 3 (4, 8.7%) and genotype 2 (1, 2.2%); Six patients in the study could not identified genotype before treatment. The median of hepatitis C virus load were 2925000UI/l (328000 - 6080000). Some baseline characteristics of the patients are presented in Table 1.

Table 1. Baseline characteristics in patients before treatment

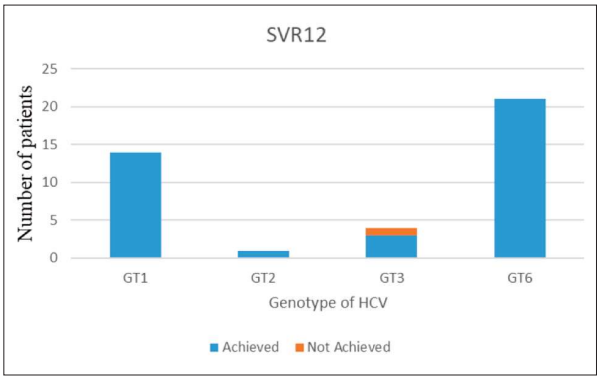
Variables		N = 46
Age (years) (Mean ± SD)		47.6 ± 22.3
Gender	Male (n,%)	32 (69.6%)
	Female (n,%)	14 (30.4%)
Total Billirubin > 17µmol/l		8 (17.4%)
Alanine Aminotransferase > 40 (U/l-37^{0}C)		31 (67.4%)
CrCl Cockroft-Gault (ml/phút)	≥ 90 (n,%)	11 (23.9%)
	50 - 89 (n,%)	24 (52.2%)
	20 - 49 (n,%)	11(23.9%)
	Median	71.3 ± 25.6
Hemoglobin (g/l) (Mean ± SD)		146.5 (140 -159)
Platelets x 109/L (Mean ± SD)		196.5 (155 -250)
Hepatitis C Virus load (Median; IQR)		2925000 (328000 - 6080000)
Genotype	1	14 (30.4%)
	6	21 (45.7%)
	2	1 (2.17%)
	3	4 (8.7%)
	No indentified	6 (13%)

The goal of treatment for chronic hepatitis C is to eliminate the hepatitis C virus from the body through a sustained viral response (SVR). When the patient achieves a sustained viral response at 12 weeks after the end of treatment, the patient is considered as cure for hepatitis C[7].

In many previous studies, the drug combination was effective in all the HCV genotypes[8]. In our study, 35/35 (100%) patients without cirrhosis and 10/11 (90.9%) patients with compensated cirrhosis achieved SVR12 support the use of the sofosbuvir/velpatasvir combination for the treatment of hepatitis C, which is also recommended in the EASL 2018 guidelines[1]. (see Table 2 and Figure 1). The observed SVR12 rates in our study are very comparable to the result of Feld et al in study ASTRAL - 1 trial that included patients with HCV genotype 1 to 6 excluding genotype 3, and reported an SVR12 rate of 99% [8]. In study of ASTRAL - 2 and ASTRAL - 3 trials reported SVR12 rate in genotype 2 and 3 as 99% and 94% respectively. In our study, 100% patients with genotype 1, 6, 2, with compensated cirrhosis and without cirrhosis achieved SVR12. Only one patient receiving treatment, whom was infected with genotype 3, had a virologic failure. He is 56 years old. His metavir score was 4 (18kpa) when started sofusbuvir/velpatavir therapy. His virus load before HCV antivirus treatment was 1.69 x 10^8UI/l. He did not achieved RVR when his HCV virus load after 4 weeks was 26.2 UI/l. He still received 12 weeks of daily sofosbuvir/velpatasvir but he lost to follow up at the time of 8 weeks and 12 weeks after the start of therapy because of Covid 19 pandemic. His HCV virus load in week 24 was 8.92 x 10^4 UI/l. Jame Wilton et al reported in a population base- corhort study that the SVR rate in genotype 3 group was 93.7%[9].

Table 2. Hepatitis C virus RNA < 15IU/mL achieved after treatment

Intention - to - treat analysis	Patients without cirrhosis (n = 35)		Patients with compensated cirrhosis (n = 11)	
	Yes, n/N (%)	No, n/N (%)	Yes, n/N (%)	No, n/N (%)
Week 4 (rapid virologic response) N = 46	34/35 (97.1%)	1/35 (2.9%)	10/11 (90.9%)	1/11 (9.1%)
Week 24 (Sustained virologic response) N = 46	35/35 (100 %)	0/35 (0%)	10/11 (90.9%)	1/11 (9.1%)



Figuere 1. Hepatitis C virus RNA < 15 IU/mL achieved in genotype group

Besides SVR12, the effectiveness of therapy was also shown by the improvement of APRI score and Metavir score. In our study, the improved of APRI score was statistically significant when compared before receiving Sofosbuvir/velpatasvir and end of treatment (Table 3). Metavir score were compared in pair at the time of begining and week 24 of started receiving HCV antivirus therapy, the improvement in liver firosis by metavir score was statistically signficant with p < 0,05 (Table 4).

Table 3. APRI score before and after 24 weeks after started antivirus treatment

	Median (IQR)	Min - Max	P
Before treatment	0.82 (0.36 - 1.64)	0.14 - 4.20	0.0001*
Week 12	0.29 (0.19 - 0.41)	0.06 - 5.71	
Week 24	0.53 (0.39 - 0.56)	0.27 - 0.59	0.1441

Table 4. Metavir score before and after 24 weeks after start antivirus treatment

	Before treatment		Week 24		P
	n	%	n	%	
F0 - F1	22	47.8	28	60.9	0.0578
F2	8	17.4	6	28.3	0.5271
F3	5	10.9	5	13.0	1
F4	11	23.9	7	10.9	0.0455*
Total	46	100	46	100	

In general, our study results depict a tolerable safety for sofosbuvir/velpatasvir among both patients without cirrhosis and patients with compensated cirrhosis as the majority of adverse events of mild severity. In our study, 15 patients complained about some symtoms which appeared after received sofosbuvir/velpatasvir therapy, such as fatigue (6/46), jaundice (1/46), ichy/ rash (2/46), insomnia (2/46). Our study results are comparable with the ASTRAL 1, 2, 3 trial. In which, the major of adverse effects were headache (22%), fatigue (15%), nausea (9%); asthenia (5%), insomnia (5%)[8]. Fazia Mir Alp et al reported that 26% patients had anemia, but in this study, they used ribavirin in decompensated cirrhotics, so anemia may caused by ribavirin[8]. In our study, 2 patients decreased platelets < 100G/l; A patient had anemia (Hb < 100g/l); leucocyte < 4G/l, total Billirubin > 17µmol/l. The adverse event profile for patients with compensated cirrhosis was consitent with that of advanced liver disease (Table 5).

CONCLUSIONS

Our study showed that the therapy of sofusbuvir/velpatasvir combination daily for 12 weeks is safe and efficacious in hepatitis C patients without cirrhosis or with compensated cirrhosis, irrespective of the genotype. Up to now, this combination therapy is one of best choices for HCV treatment.

Table 5. Adverse events and laboratory abnormalities in patients without cirrhosis and in patients with compensated cirrhosis

	Patients without cirrhosis (n = 35)	Patients with compensated cirrhosis (n = 11)
Number of patients experiencing any adverse event	3 (8.57%)	5 (45.5%)
Serious adverse event	0	0
Adverse event leading to discontinuation of Sofosbuvir/Velpatasvir	0	0
Deaths	0	0
Fatigue	1 (2.9%)	5 (45.5%)
Jaundice	0	1 (9.1%)
Ichy/Rash	1 (2.9%)	1 (9.1%)
Insomnia	1 (2.9%)	1 (9.1%)
Laboratory abnormalities in either group		
Hemoglobin < 100g/l	0	1 (9.1%)
Total leucocyte count < 4G/l	0	1 (9.1%)
Total Billirubin > 17µmol/l	1 (2.9%)	1 (9.1%)
Platelets < 100G/l	0	2 (18.2%)

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