Efficacy of Combination Sofosbuvir, Pegylated-Interferon, and Ribavirin for Treatment of Hepatitis C Virus Genotype 1 Infection in Indonesia

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ABSTRACT

Background: *The presence of direct-acting antiviral (DAA) has improved the treatment of hepatitis C virus (HCV) infection and making it more preferable than Pegylated-interferon (PegIFN) and Ribavirin (RBV) based treatment. However, treatment with all DAA combination regimen is limited and expensive in low health care affordability country including Indonesia. The appearance of generic sofosbuvir (SOF) facilitate the utilization of SOF plus PegINF with or without RBV combination. Therefore, in this study we assessed the efficacy of SOF+RBV and SOF+RBV+PegINF combination for treatment of chronic hepatitis C infections patient with genotype 1 in Indonesia.*

Method: *We performed retrospective study comprising 128 patients in Cipto Mangunkusumo Hospital with chronic hepatitis C, genotype 1, infection. Thirty six (36) patients was treated with PegINF+SOF+RBV and 92 patients was treated with SOF+RBV with the duration of therapy was 12 and 24 weeks in both arms. The primary endpoint was sustained virologic response after treatment completion (SVR12).*

Results: *In the end of treatment, 99.2% patients achieved undetected HCV RNA in 12 weeks and 24 weeks duration of therapy (100% in PegINF+SOF+RBV group and 98.9% in SOF+RBV group). The SVR12 of PegINF+SOF+RBV reach 100% meanwhile The SVR12 of SOF+RBV reach 88%. No different in SVR12 between cirrhotic and non-cirrhotic patient in PegINF+SOF+RBV group while in SOF+RBV group, the SVR12 was lower in cirrhotic patients (82.9%) compared to non-cirrhotic patients (92.2%). In multivariate analysis, HIV co-infection is associated with lower SVR12 in SOF+RBV group.*

Conclusion: *Twelve (12) weeks and 24 weeks of PegINF+SOF+RBV and SOF+RBV is effective in the treatment of genotype 1 chronic hepatitis C infection.*

Keywords: *direct-acting antiviral, hepatitis C, sofosbuvir, ribavirin, interferon*

ABSTRAK

Latar belakang: *Pemberian direct-acting antiviral (DAA) meningkatkan keberhasilan pengobatan infeksi virus hepatitis C (VHC). Dengan efikasi yang lebih tinggi dan efek samping yang minimal, DAA lebih dipilih dibandingkan dengan kombinasi Pegylated-interferon (PegIFN) dan Ribavirin (RBV). Namun kombinasi DAA seluruhnya masih terbatas dan mahal terutama di Indonesia. Sofosbuvir merupakan salah satu DAA yang tersedia dalam bentuk generik dan dapat dikombinasi dengan PegIFN dan RBV. Penelitian ini bertujuan untuk menilai efikasi kombinasi SOF+RBV dan SOF+RBV+PegINF pada infeksi VHC genotipe 1 di Indonesia.*

Metode: *Kami melakukan studi retrospektif terhadap 128 pasien infeksi VHC genotipe 1 di Rumah Sakit Cipto Mangunkusumo. Tiga puluh enam (36) pasien mendapatkan PegINF+SOF+RBV dan 92 pasien mendapatkan SOF+RBV dengan durasi terapi selama 12 dan 24 minggu pada kedua kelompok studi. Pemeriksaan muatan virus (HCV RNA) dilakukan pada saat selesai terapi (EOT) dan 12 minggu setelah selesai terapi (SVR12).*

Hasil: *Pada EOT 12 dan 14 minggu, HCV RNA tidak terdeteksi pada 99.2% pasien (100% pada kelompok PegINF+SOF+RBV dan 98.9% pada kelompok SOF+RBV). SVR12 pada kelompok PegINF+SOF+RBV mencapai 100% sementara pada kelompok SOF+RBV mencapai 88%. Tidak ada perbedaan SVR12 secara bermakan antara pasien dengan atau tanpa sirosis pada kelompok PegINF+SOF+RBV sedangkan pada kelompok SOF+RBV, SVR12 pasien dengan sirosis lebih rendah dibandingkan dengan pasien non-sirosis (82.9% vs. 92.2%). Pada analisis multivariat, ko-infeksi HIV dihubungkan dengan SVR12 yang lebih rendah pada kelompok SOF+RBV.*

Simpulan: *Pemberian terapi PegINF+SOF+RBV dan SOF+RBV selama 12 serta 24 minggu efektif terhadap infeksi VHC genotipe 1.*

Kata kunci: *direct-acting antiviral, hepatitis C, sofosbuvir, ribavirin, interferon*

INTRODUCTION

Chronic hepatitis C is a major health problem in the world. According to WHO, 3% people is infected worldwide with the prevalence is around 180 million people.[1] Hepatitis C infection is also a major health problem in Indonesia. The Indonesia Health Survey 2013 estimated that 2.5% of Indonesia People infected with hepatitis C.[2] Untreated hepatitis C virus infection will increase the risk of chronic liver diseases, cirrhosis, and liver cancer or hepatocellular carcinoma (HCC).[3]

HCV is a positive-stranded RNA-enveloped virus with six major genotypes (GTs). GT1 is the most common HCV genotype in the world comprising 46.2% of total HCV cases.[4] The similarity is also shown in Indonesia's HCV patient that GT1 being the most common HCV genotype. Furthermore, the core sequencing reveal that GT1b was the most common HCV subtype with 47.3% followed by subtype 1c with 18.7%.[5] The treatment of HCV infection has improved remarkably in the presence of direct-acting antiviral (DAA). Prior pegylated interferon based treatment has become obsolete compare to all-oral DAA treatment with higher sustain virologic response (SVR) rate and lower side effects.[6] Unfortunately, DAA based treatment is limited and expensive in low health care affordability country including in Southeast Asia.[7] This cause Pegylated interferon (PegINF) and Ribavirin (RBV) based treatment is still maintained.

However, several selected Asian Country, including Indonesia, has opportunity to use generic DAA sofosbuvir with more affordable price. Sofosbuvir (SOF) is a HCV NS5B polymerase inhibitor that was recently approved for treatment of chronic HCV genotypes 1 to 4. Addition SOF to RBV with or without PEG will improve the SVR rate up to 50-90%.[8] Nonetheless, with majority of genotype 1 infections, the combination of SOF with PEG/RBV is no longer mentioned in some of the guidelines where other DAAs combination is more favorable for genotype 1, such as sofosbuvir/ledipasvir combination.[9] Despite no longer stated in the recent guideline, combination of SOF+RBV with or without PegINF are remain used in treatment of chronic HCV with genotype 1 in Indonesia. With limited study available for this regiment particularly for genotype 1, we concluded that further study is needed. Therefore, in this study we assessed the efficacy of SOF+RBV and SOF+RBV+PegINF combination for treatment of chronic hepatitis C infections patient with genotype 1 in Indonesia.

METHOD

We performed retrospective cohort study of patients ≥ 18 years of age diagnosed with HCV genotype 1 infection at the hepatobiliary clinic, Cipto Mangunkusumo Hospital, between 2016 and 2017. Treatment-naive and treatment experienced who received Sofosbuvir plus Ribavirin and Sofosbuvir plus Pegylated interferon and Ribavirin were included in this study.

Patient's data were collected from hospital health record including patient demographics, baseline laboratory data, treatment history, presence of cirhosis, HCV genotype and baseline HCV-RNA. Cirrhosis was diagnosed by biopsy or by transient elastography (> 12.5 kPa). Patients with initial viral load more than 8 x 10^5 IU/mL were considered as high viral load. Patient data were followed retrospectively through treatment duration. HCV RNA data at the end of treatment (EOT)

duration were collected. The primary point of this study are the absence of detectable HCR RNA in serum 12 week (SVR12) and 24 week (SVR24) after treatment duration. Patients whose data were not complete were considered as lost-to-follow-up. Any discharge of therapy due to adverse events and death were reported. This study was approved by the Institutional Review Board at Faculty of Medicine Universitas Indonesia (No. Protocol: 17-12-1208).

Univariate analysis were performed to identify factors associated with SVR12. Variables which included in univariate analysis were patient's demographic characteristic, HIV and HBV co-infections, cirrhosis, and baseline viral load. A $p < 0.05$ was considered statistically significant. All analysis was performed using SPSS version 22 (IBM Corporation, New York, NY).

RESULTS

From 2016 through 2017, 128 patients were enrolled in this study. Thirty six (36) patients were received SOF+RBV+PEG IFN and 92 patients received SOF+RBV. Seventy four (74) patients (57.8%) were male and mean age of all participants was 53. All patients were Asians with 96.1% were Chinese and 3.9% were Indonesian. Median initial viral load of all regimens was 1.53 x 10^6. Initial high viral load was identified in 80.6% in SOF+RBV+PEG INF group and 58.7% in SOF+RBV group. In sub genotype analysis, most of the patients had genotype 1 who's the sub genotype had not been identified and labeled as undeterm. Sub genotype 1b and 1a followed by 28.1% and 24.2%. Forty eight (48) patients were cirrhotic that 7 patients in SOF+RBV+PEG IFN group and 41 patients in SOF + RBV group. Total 4 patients had HIV co-infection, 1 patient in SOF+RBV+PEG IFN group and 3 patients in SOF+RBV group. In SOF+RBV+PEG IFN group, 28 patiens (77.8%) had 12 weeks of treatment duration and 8 patients (22.2%) in 24 weeks. In SOF+RBV group, 44 patients (47.8%) had 12 weeks of duration and 48 patients (52.2%) in 24 weeks (Table 1).

In the end of treatment (EOT), 99.2% patients achieved undetected HCV RNA in 12 weeks and 24 weeks duration of therapy (100% in PegINF+SOF+RBV group and 98.9% in SOF+RBV group). All 36 (100%) patients treated with SOF+RBV+PegIFN reached SVR12 meanwhile 81/92 patients (88%) treated with SOF+RBV reached SVR12. Overall SVR12 of patients with HCV genotype 1 treated with combination of SOF plus RBV with/without PegIFN were 91.4% (Figure 1).

In multivariate analysis, HIV co-infection is associated with lower SVR in SOF+RBV group (OR = 0.05; 95% CI = 0.01-0.67) where all the 3 HIV co-infected patients failed to reach SVR12 (Table 2).

Table 1. Characteristic demographic and clinical baseline patients hepatitis C genotype 1

	Overall (n = 128)	SOF + RBV + PEG IFN (n = 36)	SOF + RBV (n = 92)
Demographic			
Number of patients (%)	128 (100%)	36 (28.1%)	92 (71.9%)
Male sex – n (%)	74 (57.8%)	27 (75%)	47 (51.1%)
Age – mean (range)	53 (27-82)	42 (32-74)	58 (27-82)
Race, n (%)			
Indonesian	123 (96.1%)	35 (97.2%)	88 (95.7%)
Chinese	5 (3.9%)	1 (2.8%)	4 (4.3%)
Clinical Baseline			
Initial Viral load IU/ mL – median (range)	1.53 x 10^6 (6.5 x 10^1 – 5.7 x 10^9)	2.51 x 10^6 (1.9 x 10^2 – 2.9 x 10^7)	1.53 x 10^6 (6.5 x 10^1 – 5.7 x 10^9)
Initial High Viral load IU/ mL – n (%)	83 (64.8%)	29 (80.6%)	54 (58.7%)
Sub Genotype, n (%)			
1a	31 (24.2%)	8 (22.2%)	23 (25%)
1b	36 (28.1%)	10 (27.8%)	26 (28.3%)
1c	5 (3.9%)	2 (5.6%)	3 (3.3%)
1d	1 (0.8%)	0 (0%)	1 (1.1%)
Undeterm 1	55 (43%)	16 (44.4%)	39 (42.4%)
Median AST (range) – U/L	59 (17-395)	59 (17-191)	59 (20-395)
Median ALT (range) – U/L	62 (8-303)	62 (8-303)	62 (11-228)
Presence of Cirrhosis – n (%)	48 (37.5%)	7 (19.4%)	41 (44.6%)
Presence of HIV – n (%)	3 (2.3%)	1 (2.8%)	2 (2.1%)
Duration of Treatment, n (%)			
12 weeks	72 (56.3%)	28 (77.8%)	44 (47.8%)
24 weeks	56 (43.8%)	8 (22.2%)	48 (52.2%)

Table 2. Bivariate analysis baseline characteristics of SVR in sofosbuvir plus ribavirin group

Baseline characteristic	Odds ratio (OR)	95% confidence linterval	p
Gender: male vs. female	1.79	(0.48–6.60)	0.524
Age: ≥ 40 vs. <40	0.31	(0.04-2.53)	0.446
Low viral Load vs. high viral load	2.82	(0.76-10.43)	0.190
Cirrhosis	0.41	(0.11-1.52)	0.208
HIV co-infection	0.1	(0.05-0.19)	0.013

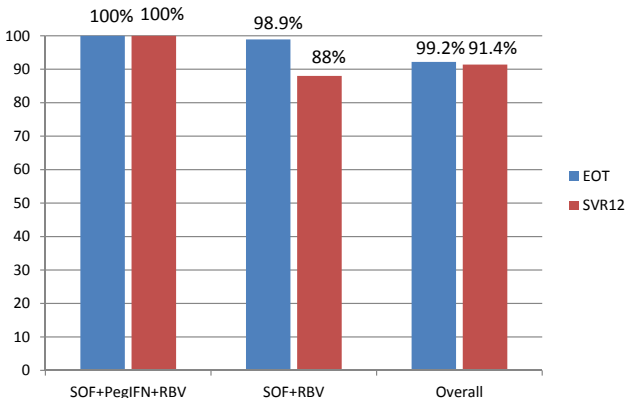

Figure 1. Undetectable HCV RNA in the end of treatment (EOT) and SVR12

DISCUSSION

In this study, combination of Sofosbuvir plus ribavirin with/without PegIFN for 12 and 24 weeks led to high rates of sustained virological response in patients with HCV genotype 1 infection. Regimen of Sofosbuvir plus Ribavirin plus PegIFN show excellent effectiveness with 100% of SVR12 rate including patients with high intial viral load, cirrhosis, and HIV co-infections regardless the duration of therapy. Nonetheless, combination Sofosbuvir and Ribavirin also showed high rates of SVR12 with 88%.

This study shows that the combination of Sofosbuvir plus Ribavirin had high SVR12 of 88% and 98.9% undetected of HCV RNA in the end of treatment. No significant different in duration of therapy with 12 weeks and 24 weeks as well as cirrhosis status of the patients. However, Sofosbuvir and Ribavirin treatment has less effectiveness in patients with HIV co-infections which all 3 patients failed to reach SVR12. Study by Lai et al showed excellent SVR of Sofosbuvir plus Ribavirin in Asian population with HCV genotype 1 infection. Twenty (20) patient with HCVgenotype 1b infection treating with Sofosbuvir plus Ribavirin achieved high rates of SVR12, 100% for 12 and 16 weeks therapy and 83% with 24 weeks therapy.[10]

Another study comprising sofosbuvir with Ribavirin in HCV genotype 1 patients by Gane et al showed relatively high SVR24 weeks in treatment-naive patients with 84% (21/25). However, this regiment is less effective with treatment-experienced patients that only 10% achieved SVR24.[11] Compared to HCV genotype 2 and 3, Sofosbuvir plus Ribavirin showed less efficacy in genotype 1 in achieving SVR24 yet all groups showed similar viral kinetics characteristic that all patients had an undetectable level of HCV RNA by week 4. This identical virologic response in all treatment groups was showed regardless of genotype, treatment history, baseline viral load, race, ethnic group, IL28B status, and presence of interferon in regimen. However, in genotype 1 HCV and treatment experienced patients, this virologic response did not sustain.

However, combination of sofosbuvir and ribavirin for genotype 1 showed less effectiveness with SVR range from 47% to 84% in various study.[12,13] A randomized clinical trial study by Osinusi et al show the efficacy and safety of sofosbuvir with weight-based or low-dose ribavirin with 60 treatment-naive hepatitis C genotype 1 patients. The SVR24 of this study are 68% for weight-based and 48% for low-dose Ribavirin. This study identified association between male sex, advanced liver disease, and high baseline HCV RNA with viral relapse. 54% participants with advanced liver diseases relaps in this study.[14]

A network meta-analysis performed by WHO show that Sofosbuvir plus Ribavirin in genotype 1 and 4 HCV infection has SVR12 of 77.26% (95% CI: 67.98 , 86.54) in treatment-naive and 75.46% (95% CI: 53.94, 96.98) in treatment-experienced patients.[1]

This mixed result and the appearance of other more effective DAA making the combination of Sofosbuvir and Ribavirin is no longer recommended in several guidelines for HCV genotype 1. However, Ribavirin is widely available and remains to be a treatment option, in combination with Sofosbuvir, for genotype 1 HCV infection in Indonesia while other DAA's combinations is limited and expensive.

In this study, 36 patients were treated with SOF+RBV+PEG IFN and all patients reached SVR12 (100%) regardless of the baseline viral load, cirrhosis status, co-infection, and duration of therapy (12 and 24 weeks). Recent systematic review and meta-analysis by Dolatimehr et al also showed that combination of SOF+RBV+PegIFN is effective for HCV genotype 1 infection. Total of 5 articles and sample size of 411 result in 88.54% of pooled SVR rate (95% CI: 85.77–91.32%).[15]

Different than the combination of sofosbuvir and ribavirin, several studies show relatively similar range of effectiveness in sofosbuvir plus peg-interferin plus ribavirin combination. In Neutrino phase 3 study, SOF+PegIFN+RBV had overall SVR12 of 89% which 92% in sub genotype 1a and 82% in subgenotype 1b.[16] In HCV TARGET 2.0 study, this regimen had SVR4 of 85% whereas in TRIO study, this regimen reached 81% of SVR12.[17,18] In these study, cirrhosis status of the patients correlated with lower SVR. Despite this combination is no longer recommended due to the presence of all oral regimen, combination of sofosbuvir plus Peg-Interferon plus ribavirin showed excellent effectiveness in HVC genotype 1 infections. Moreover, this regimen also effective against other unfavorable characteristic such as cirrhosis patients, high baseline viral load, and co-infection. This regimen is also effective both in 12 and 24 weeks of therapy.

There are some limititation in our study such as no complete adverse event data, lack of treatment history data, and no data of IL28B which may affect our result. We hope that in the future more study will be performed with more complete data.

CONCLUSSION

This study showed that 12 weeks and 24 weeks of PegINF+SOF+RBV and SOF+RBV is effective in the treatment of genotype 1 chronic hepatitis C infection. Despite these regimen is no longer recommended in several guidelines, these regimen are effective as alternative to all oral DAAs treatment which can be difficult to access and expensive in HCV genotype 1 infection.

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