Decreased Liver Fibrosis in Patients with Hepatitis C Virus (HCV)/Human Immunodeficiency Virus (HIV) Coinfection After Treatment with Sofosbuvir/Daclatasvir

Andreas Jonathan, Rudi Wisaksana**, Nenny Agustanti****

*Department of Internal Medicine, Faculty of Medicine
Universitas Padjajaran/Dr. Hasan Sadikin General Hospital, Bandung
** Division of Infectious and Tropical Disease, Department of Internal Medicine
Faculty of Medicine, Universitas Padjajaran/Dr. Hasan Sadikin General Hospital, Bandung
*** Division of Gastroentero-hepatology, Department of Internal Medicine
Faculty of Medicine, Universitas Padjajaran/Dr. Hasan Sadikin General Hospital, Bandung

Corresponding author:
Rudi Wisaksana. Division of Infectious and Tropical Disease, Department of Internal Medicine, Hasan Sadikin General Hospital. Phone: +62-22-2040151; facsimile: +62-22-2038986. E-mail: rudiw98@gmail.com

ABSTRACT

Background: *Hepatitis C Virus (HCV)/Human Immunodeficiency Virus (HIV) co-infection increases the progression of liver fibrosis to advanced liver disease and death. The aim of this study is to determine whether decreased of liver fibrosis occur in HCV/HIV coinfection patients after therapy with Sofosbuvir/Daclatasvir.*

Method: *This study used a quasi-experimental study design without a control group. The study subjects were HCV/HIV coinfection patients who received Sofosbuvir/Daclatasvir therapy in the Gastroentero-hepatology Clinic of Dr. Hasan Sadikin Hospital. In this study measurement of liver fibrosis was carried out by using AST to platelet ratio index (APRI) and fibrosis-4 index (FIB-4) before therapy and when sustained virological response at 24 weeks (SVR-24) was achieved.*

Results: *The study involved 29 subjects. Most of the research subjects were men, with an average age of 40.38 years (SD 3.48). From the results of this study, we found a decrease in APRI scores and FIB-4 index when HCV/HIV coinfection patients, that were treated with Sofosbuvir/Daclatasvir, achieved SVR 24. The median of APRI scores before therapy and after SVR-24 was decreased from 0.41 to 0.28 (95% CI: 0.01 - 0.23; p = 0,01) and the median of FIB-4 Index before therapy and after the SVR 24 was decreased from 0.94 to 0.81 (95% CI: -0, 04 - 0.35; p = 0.28).*

Conclusion: *This study concluded that therapy using Sofosbuvir/Daclatasvir in HCV/HIV coinfected patients has very good effectiveness and can reduce liver fibrosis.*

Keywords: *HCV/HIV coinfection, liver fibrosis, Sofosbuvir/Daclatasvir*

ABSTRAK

Latar belakang: *Koinfeksi Hepatitis C Virus (HCV)/ Human Immunodeficiency Virus (HIV) meningkatkan progresifitas fibrosis hati menjadi penyakit hati lanjut dan kematian. Penelitian ini bertujuan untuk mengetahui apakah terjadi penurunan fibrosis hati pada pasien koinfeksi HCV/HIV setelah diberikan terapi dengan Sofosbuvir/Daclatasvir.*

Metode: *Penelitian ini menggunakan rancangan penelitian kuasi eksperimen tanpa grup kontrol. Subjek penelitian adalah pasien koinfeksi HCV/HIV yang mendapatkan terapi Sofosbuvir/Daclatasvir di Unit Rawat*

Jalan Poli Gastroentero-hepatologi Rumah Sakit Dr. Hasan Sadikin. Pada subjek penelitian dilakukan pengukuran fibrosis hati menggunakan Skor AST to platelet ratio index (APRI) dan indeks fibrosis-4 (FIB-4) sebelum terapi dan saat SVR-24.

***Hasil:** Jumlah subjek penelitian sebanyak 29 orang. Sebagian besar subjek penelitian adalah laki-laki, dengan rerata usia 40,38 tahun (SD 3,48). Angka keberhasilan Sofosbuvir/Daclatasvir mencapai sustained virological response at 24 weeks (SVR-24) pada penelitian ini mencapai 97%. Dari hasil penelitian ini didapatkan penurunan skor APRI dan Indeks FIB-4 saat pasien koinfeksi HCV/HIV yang diterapi Sofosbuvir/Daclatasvir mencapai SVR 24. Terjadi penurunan skor APRI sebelum terapi dan setelah SVR- 24 dari 0,41 menjadi 0,28, perubahan sebesar 0,13 (95% CI: 0,01 – 0,23) dan penurunan Indeks FIB-4 sebelum terapi dan setelah SVR 24 dari 0,94 menjadi 0,81, perubahan sebesar 0,13 (95% CI: -0,04 – 0,35).*

***Simpulan:** Penelitian ini menyimpulkan bahwa terapi dengan menggunakan Sofosbuvir/Daclatasvir pada pasien koinfeksi HCV/HIV memiliki efektivitas yang sangat baik dan dapat menurunkan fibrosis hati.*

***Kata kunci:** Koinfeksi HCV/HIV, fibrosis hati, Sofosbuvir/Daclatasvir*

INTRODUCTION

The number of patients infected with Hepatitis C Virus (HCV) in the world remains quite high. It is estimated that approximately 130-170 million people are infected by HCV with 10-30% suffering from coinfection with human immunodeficiency virus (HIV).[1,2] This shows that HCV is a global health problem and becomes one of the main causes of advanced stage liver disease or even death.[1-3] HCV/HIV coinfection can accelerate the occurrence of liver fibrosis; hence, liver disease is currently one of the main causes of death in patients with HIV infection with 30-50% HIV patients died due to terminal stage liver disease.[3-8] The decreased number of CD4 and dysregulation of CD4 function causes the diminishing effect of anti fibrosis and increased secretion of profibrosis cytokines, which result in the acceleration of the occurrence of liver fibrosis in patients with HCV/HIV coinfection.[5,9,10]

Liver biopsy is currently the gold standard in determining the degree of liver fibrosis, yet liver biopsy also has several drawbacks as this procedure often causes a range of complications, the cost is quite expensive, subjective, and it often causes sampling error.[11,12] Due to these drawbacks, a non-invasive method is developed to evaluate liver fibrosis. The non-invasive marker from the blood which was claimed as a substitute liver biopsy is AST/platelet ratio (APRI) and FIB-4.[12]

In almost two decades, combination of interferon (IFN) and ribavirin treatment is the single available option for patients with HCV infection with low rate of sustained virological response (SVR), particularly in patients with HCV/HIV coinfection,[1,3] where the SVR rate was only about 30%.[13] Direct-acting antivirals (DAAs) is a new drug, which was proven to increase SVR rate and decrease morbidity or mortality rate that is associated with HCV infection. Additionally, DAAs is proven to be safe to be used in patients with HCV monoinfection or HCV/HIV coinfection.[2,3,14] In this study, we will evaluate the reduction of liver fibrosis after treatment using DAAs in HCV/HIV co-infected patients.

METHOD

The accessible population was HCV/HIV co-infected patients who received Sofosbuvir/Daclatasvir in Gastroentero-hepatology Outpatient Polyclinic in Hasan Sadikin Hospital in 2017-2018 with inclusion criteria of aged more than 18 years, treated with Sofosbuvir/Daclatasvir and had laboratory data of complete blood count, serum aspartate aminotransferase (AST)/serum alanine aminotransferase (ALT) before and during SVR 24, positive Anti HIV, detected HCV RNA before treatment. Exclusion criteria of this study were patients who suffered co-infection with hepatitis B virus (HBV), those who did not complete treatment according to the time planned and failed to achieve SVR-24.

This study was an analytic study with quasi-experimental design without control group (pretest-posttest), using primary and secondary data in Gastroentero-hepatology Outpatient Polyclinic. Quasi experiment is a study to estimate the effect due to an intervention without randomization.[15] In the single group pretest-posttest design, initial measurement was performed to all samples, intervention was applied to those samples, and a repeat measurement was performed in the same set of sample after intervention.[16] In this study, the sample size was determined using mean difference in one paired group formula, requiring a sample size of minimum 22 people. Sample size calculation was based on the study performed by Shiffman et al.[17,18]

Data which would be collected was changes of liver fibrosis in patients with HCV/HIV coinfection before and after Sofosbuvir/Daclatasvir treatment which consisted of primary and secondary data, obtained from patients who seek for treatment in Gastroentero-hepatology Outpatient Polyclinic Hasan Sadikin Hospital. Secondary data being collected was liver fibrosis before Sofosbuvir/Daclatasvir treatment, which was assessed using APRI score and FIB-4 index, in 2017 and 2018. APRI score was calculated using the formula as follows: (AST/ *upper limit of normal*) / trombocyte (10^9/ L) × 100, meanwhile FIB-4 index was calculated using the formula: *[age (year) × AST (U/L)] /[PLT (10^9/L) × ALT (U/L) $^{1/2}$]*. The treatment duration with Sofosbuvir/Daclatasvir was based on the APRI score; if the value was < 1, treatment would be administered for 12 weeks; if the value was ≥ 1, treatment would be administed for 24 weeks. Liver fibrosis, which had been quantified using APRI score and FIB-4 index, was re-assessed at 24 weeks after treatment completion.

Statistical analysis would be selected according to the objective of the study and the proposed hypothesis. Before univariate analysis was performed, normality test of numerical data was conducted using *Shapiro Wilk test* for data less than 50 people; hence it was known that data was normally distributed or not. If the p value is > 0.05, the data is normally distributed, but if p value is ≤ 0,05, then the data is not normally distributed.

Univariate analysis was intended to illustrate the characteristics of study subjects which included age, sex, complete blood count, AST, ALT, HCV RNA, liver fibrosis calculation with APRI score and FIB-4 index before treatment. Description of basic characteristics were presented in sum and percentage for categorical data, while for numerical data it depends on the data distribution. If the data is normally distributed, univariate analysis is stated in mean and standard deviation, but if the sample is not normally distribiyed, then it is stated in median with the range.[19]

Bivariate analysis to assess the change of liver fibrosis in HCV/HIV coinfected population between before and after Sofosbuvir/Daclatasvir treatment was performed using parametric method, particularly *dependent t test*, if data is normally distributed, if the data is not normally distributed, the analysis will be performed using non-parametric method, the Wilcoxon sign Rank test. Data analysis was performed using statistical product and service solution (SPSS) software for Windows version 22.0 with a confidence interval of 95%.

RESULTS

This study was performed in Gastroentero-Hepatology Outpatient Clinic of Dr. Hasan Sadikin Hospital, Bandung in the year 2017-2018. Study subjects were patients with HCV/HIV coinfection who received Sofosbuvir/Daclatasvir and fulfilled the inclusion and exclusion criteria.

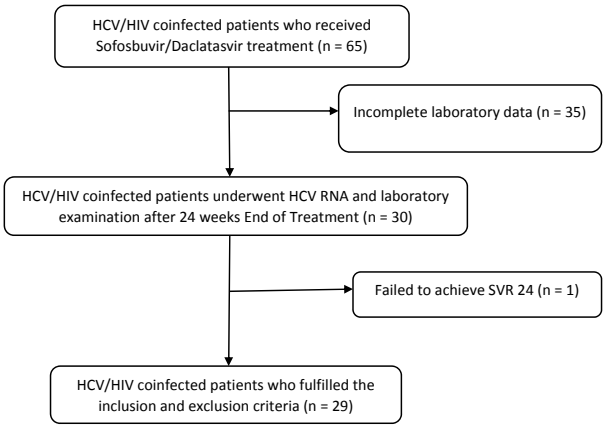

Figure 1. Flowchart of the study results

There were 65 patients who suffered from HCV/HIV coinfection who were treated with Sofosbuvir/Daclatasvir in Gastroentero-hepatology Outpatient Clinic of Dr. Hasan Sadikin Hospital and all patients have completed the treatment. Two patients were excluded from this study because they did not have the complete baseline laboratory data, while 33 patients were also excluded from the study because they did not come in week 24 after completion of treatment for the evaluation of HCV-RNA and other laboratory tests. From 33 patients who did not come in week 24 after completion of treatment, 2 patients did not answer the short text message or phonecall, while the other 31 patients answered the message but unable to attend. There were 30 patients with complete laboratory data, but 1 patient failed to achive SVR; thus, patients who fulfilled the inclusion and exclusion criteria were 29 patients.

Characteristics of study subjects based on sex and age of HCV/HIV co-infected patients who received Sofosbuvir/Daclatasvir in Gastroentero-Hepatolog Outpatient Clinic of dr. Hasan Sadikin Hospital can be seen in Table 1.

The median of APRI score before treatment was 0.41 (0.12-2.13) while the median value of FIB-4 was 0.94 (0.47-2.55). APRI score < 1 was observed in 25 people (86.2%), while the score ≥ 1 was observed in 4 people (13.8%). FIB-4 value of < 1,45 was observed in 23 people (79.3%), meanwhile the FIB-4 value of ≥ 1,45 was observed in 6 people (20,7%).

Table 1. Characteristics of study subjects (n = 29)

Variable	n (%)	Mean (SD)	Median (min-max)
Age (years)			
≤ 35	3 (10.3)	40.38	
35-45	24 (82.8)	(3.478)	
≥ 45	2 (6.9)		
Sex			
Male	22 (75.9)		
Female	7 (24.1)		
IDU			
AST (U/L)	29 (100)		40.0 (14-172)
ALT (U/L)			41.0 (9-310)
Platelet (10^3/mm^3)			
Albumin (g/dl)			4.31 (3.25-5.07)
HCV RNA		243 (65,9)	2.57 E06 (<10-1.20E07)
Positive	29 (100)		
Negative	0 (0)		
APRI			
<1	25 (86.2)		0.41 (0.12-2.13)
1-2	2 (6.9)		
>2	2 (6.9)		
FIB-4			
<1.45	23 (79.3)		0.94 (0.47-2.55)
1.45-3.25	6 (20.7)		
> 3.25	0		

IDU: injecting drug use, AST: aspartate aminotransferase, ALT: alanine aminotransferase, HCV RNA: hepatitis C virus ribonucleic acid, APRI: aspartate aminotransferase to platelet ratio index, FIB-4: fibrosis-4

A total of 36 patients was excluded from this study. The average age of patient being excluded was 39.14 (SD: 3.34), consisted of 28 male patients (78%) and 8 female patients (22%). From 36 patients being excluded, 34 patients had complete laboratory data. The median APRI score and FIB-4 index from these patients before sofosbuvir/daclatasvir treatment was 0.40 (0.18-4.2) and 0.76 (0.3-8.43). APRI score < 1 was observed in 27 patients (79%) and APRI ≥ 1 was observed in 7 patients (21%). FIB-4 < 1,45 was obserbed in 26 patients (76%) and FIB-4 ≥ 1,45 was found in 8 patients (24%).

Bivariate analysis was performed to analyse the change of liver fibrosis in HCV/HIV co-infected patients before and after Sofosbuvir/Daclatasvir treatment using a non-parametric method, the Wilcoxon sign rank test, because the data was not normally distributed. The difference of APRI score and FIB-4 index in HCV/HIV co-infected patients before and after Sofosbuvir/Daclatasvir treatment in Gastroentero-hepatology Outpatient Clinic of Dr. Hasan Sadikin Hospital can be seen in Table 2.

In Table 2 it could be seen that there was a significant decrease of AST and ALT after sofosbuvir/daclatasvir treatment. Trombocytes was relatively unchanged, while there was a decrease in albumin value after sofosbuvir/daclatasvir treatment.

Table 2. The difference of thrombocyte, albumin, AST, and ALT values with the use of treatment

Variables	Before treatment	During SVR 24	p
AST (U/L)	40 (14 – 172)	24 (11 – 55)	**< 0.001[b]***
ALT (U/L)	41 (9 – 310)	26 (16 – 69)	**0.001[b]***
Trombocyte (10^3/mm^3)	242 (65)	243.3 (55,4)	0.965[a]
Albumin (g/dL)	4.32 (3.25 – 5.07)	4.20 (3.60 – 5.00)	**0.021[b]***

Notes: Analysis was performed using [a]t-test, [b]Wilcoxon test, *significant p < 0.05. AST: aspartate aminotransferase, ALT: alanine aminotransferase, SVR: sustained virological response

Table 3. APRI score and FIB-4 index before and after treatment

Variables	Before treatment	After SVR 24	Difference	p
	Median (min – max)	Median (min – max)	Median (95% CI)	
APRI score	0.41 (0.12 – 2.13)	0.28 (0.09 – 0.75)	0.13 (0/01 – 0.23)	0.001*
FIB-4 index	0.94 (0.47 – 2.55)	0.81 (0.36 – 1.56)	0.13 (-0.04 – 0.35)	0.028*

Note: Analysis was performed using Wilcoxon test, *significant p < 0,05. APRI: aspartate aminotransferase to platelet ratio index, FIB-4: Fibrosis-4, SVR: sustained virologic response

From the aforementioned analysis results, it was found that there was a decrease in APRI score and FIB-4 index when HCV/HIV co-infected patients who were treated with Sofosbuvir/Daclatasvir achieved SVR 24 with APRI score before and after therapy from 0.41 to 0.28. The change was 0.13 (95% CI: 0.01 – 0.23), which based on statistical analysis showed significant difference. The FIB-4 index before and after treatment from 0.94 to 0.81. The change was 0.13 (95% CI: -0.04 – 0.35), which based on statistical analysis showed significant difference.

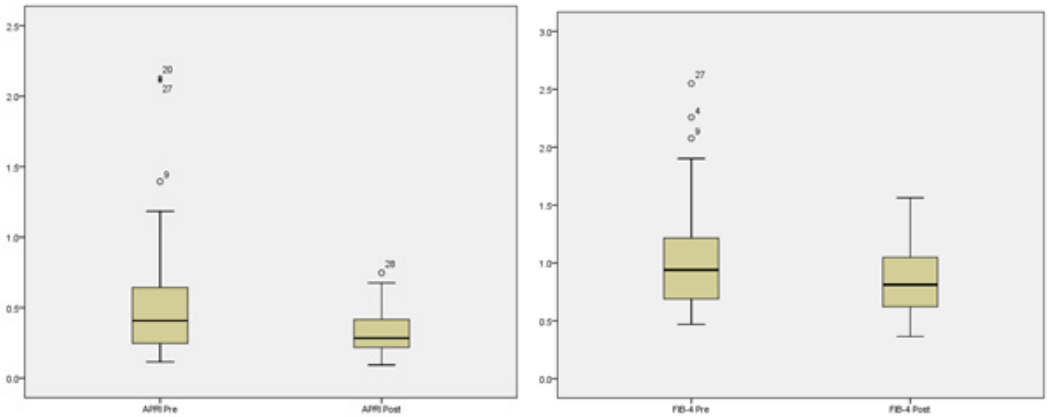

Figure 2. Boxplot changes of APRI score and FIB-4 before and after treatment

Before sofosbuvir/daclatasvir treatment, there were 25 (86.2%) patients with APRI score < 1.4 patients (13.8%) with APRI score ≥1. After sofosbuvir/daclatasvir treatment, all HCV/HIV co-infected patients had APRI score < 1. Twenty-three (79.3%) patients had FIB 4 index of < 1.45, 6 (20.7%) patients had FIB 4 index of ≥ 1.45 before being treated with Sofosbuvir/Daclatasvir. Meanwhile, after treatment 28 patients (96.5%) has FIB 4 index of < 1.45 and 1 patient (3.5%) had FIB-4 index of ≥ 1.45.

DISCUSSION

In this study, 22 (75.9%) subjects were male. The results of this study was in accordance with the epidemiologic data of HIV patients in Teratai Polyclinic Hasan Sadikin Hospital in 2007 which was dominated by male, 68% from 611 HIV patients.[20] HIV cohort study in Asia reported HCV/HIV co-infected patients were 85% male from 794 HCV/HIV coinfected patients being studied.[21] A study performed by Nunes et al showed HCV/HIV coinfected patients was 71% male from 207 patients being studied and a study by Sanvisens et al stated 81.5% from 243 HCV/HIV coinfected patients were male.[22,23] Bansal stated that male who were infected with HCV often developed into liver fibrosis and cirrhosis.[9] As stated by Rollet-Kurhajec, this was possible due to the presence of estrogen hormone in female which inhibit the proliferation of stellate cells that has protective effect in the liver.[7]

The mean age of HCV/HIV coinfected patients in this study was 40.38 years (SD: 3.478). This result was different from the epidemiologic data of young-aged male HIV patients with IDU history in Teratai Polyclinic Hasan Sadikin Hospital year 2007 (median age 28 years).[20] The majority of the sample in this study was existing patients who were included in the study in Teratai Polyclinic Hasan Sadikin Hospital in 2007, with 21 patients (72%) were diagnosed with HIV before 2007 and 8 patients (28%) were diagnosed with HIV after 2007. Several epidemiologic data showed the same results with variable median and age range. A study by Sanvisens et al[23] found that the median age of HCV/HIV coinfected patients was 31 years with an age range of 27-35 years, TAHOD cohort study by Chen et al reported the age range of study subjects was 40-50 years, and the study by Kirk et al showed a median age of 49 years.[6,21] Bansal et al stated that the progression of liver fibrosis into cirrhosis was associated with advanced age during infection, increased in accordance to the duration of HCV infection, and one third of patients developed into cirrhosis after 13 years being infected with hepatitis virus.[9] Dusheiko stated that cirrhosis was found in 2% patients who were infected with HCV at the age of < 20 years, 6% patients infected with HCV at the age of 31-40 years, 37% patients were infected with HCV at the age of 41-50 years, and 63% patients infected with HCV at the age of > 50 years.[24] Old age might be associated with the shortening of hepatocyte telomere that results in the decrease of function and regeneration ability of the hepatocyte.[25]

The success rate of Sofosbuvir/Daclatasvir to achieve SVR-24 in HCV/HIV coinfected patients in di Gastroentero-hepatologi Clinic of Hasan Sadikin Hospital was 97%. This result was similar to that of previous study performed by Wyles et al.[26] HCV RNA examination after treatment in this study was performed in week 24 after completion of treatment (SVR-24), although based on the National Consensus of Hepatitis C Management in Indonesia year 2017 (*Konsensus Nasional Penatalaksanaan Hepatitis C di Indonesia tahun 2017*) SVR-24 was more appropriate for patients receiving interferon therapy; while patients who received DAAs therapy can use SVR-12.[27] In the study by Chen et al there was a conformity between SVR-12 and SVR-24. Hence, both modalities could be used to determine recovery of HCV patients.[28]

In this study, there were 4 study subjects who suffered from liver cirrhosis. This was shown from the calculation of APRI score particularly in 25 (86.2%) subjects who had APRI score < 1 and 4 (13.8%) subjects who had APRI score ≥1, with a median of 0.40 with minimum value of 0.12 and a maximum value of 2.13. Majority study subjects experienced mild liver fibrosis where from the calculation of FIB-4 index, 23 subjects (79.3%) had mild liver fibrosis with a score of < 1.45, 6 (20.7%) subjects had severe liver fibrosis with FIB-4 index value of ≥1.45, with a median FIB-4 index of 0.81 with a minimum value of 0.36 and a maximum value of 1.56. In the study conducted by Widiayati et al in Teratai Polyclinic Dr. Hasan Sadikin Hospital, the results of the study were not of much difference. Most study subjects (80.5%) had mild liver fibrosis, 14.4% had severe liver fibrosis and 5.1% had cirrhosis.[12] In another study performed by Salmon et al different results were observed. From 53 HCV/HIV coinfected study subjects, 18 (34%) patients suffered from cirrhosis with a median FIB-4 index value of 2.01 (1.32-2.59).[29] A study conducted in Egypt by Mehrez et al in HCV/HIV coinfected patients found a quite high mean value of FIB-4 of

1.97 with a standard deviation of 1.38.[12] Labarga et al who perfomed a Fibroscan examination in HCV/HIV coinfected patients, found that 33.3% from 138 sample suffered from severe liver fibrosis (F3-F4).[30] HCV/HIV coinfection may accelerate the development of liver fibrosis. Therefore, until recently liver disease is one of the highest mortality causes in HIV infected patients with 30-50% HIV patients died due to terminal stage liver disease.[3-8] The decrease of CD4 number and dysregulation of CD4 function causes the decrease of anti fibrosis effect and an increase of profibrosis cytokine secretion which may lead to the acceleration of development of liver fibrosis in HCV/HIV coinfected patients.[5,9,10]

In this study, there was a decrease in AST and ALT after treatment with Sofosbuvir/daclatasvir, each from a median of 40 and 41 to 24 and 26. This result was in accordance with previous study performed by Khan et al which stated AST and ALT decreased significantly in hepatitis C patients who achieved SVR after treatment with DAAs.[31]

Thrombocyte values in this study did not differ significantly after Sofosbuvir/Daclatasvir therapy. This result was slightly different from previous study by Kwong et al which stated that SVR in HCV monoinfected patient might increase platelet value significantly. In this study, platelet values did not change as the mean thrombocyte before treatment was quite high, particularly 243.000/mm^3 with a standard deviation of 65.900/mm^3, while in the study of Kwong et al the mean platelet was 172.000/mm^3 with a standard deviation of 56.000/mm^3. In the study conducted by Kwong et al, it was stated that the increase in thrombocyte values occurred particularly in patient with thrombocyte values of less than 150.000/mm^3 before treatment. In patient with cirrhosis or severe fibrosis the platelet value was correlated with histologic abnormalities of the liver and portal pressure. The change in platelet value after patient achieved SVR in chronic hepatitis C patient was associated with degree of liver fibrosis.[32]

Albumin is produced by the liver and will decrease in the presence of liver cirrhosis. In this study there was a decrease in albumin before and after Sofosbuvir/Daclatasvir treatment from a median of 4.32 before treatment to 4.20 after treatment. Results of this study were different from those of Kan et al who observed the presence of albumin increase in HCV monoinfected patients achieving SVR 24 after treatment with Daclatasvir/Asunaprevir (DAAs). However, in the same study it was also stated that the increase of albumin was only observed in patients with albumin value of less than 4 g/dL before treatment. In patients with albumin levels of more than 4 g/dL, there was no significant difference before and after achieving SVR 24.[33] The change of albumin value could be caused by the disruption of production causing malnutrition, malabsorption or cirrhosis and increase of excretion which often happen in nephropathy/enteropathy.[34] In this study, we did not know the nutritional status, kidney function or gastrointestinal complaints of the participants, as these factors may influence the albumin value.

APRI score decreases after HCV/HIV coinfected patients were treated with Sofosbuvir/daclatasvir until achieving SVR 24 as shown by a decrease in median value before and after therapy from 0,41 to 0,28, a change of 0,13 (95% CI: 0,01-0,23). Before treatment with Sofosbuvir/Daclatasvir, there was 4 cirrhosis patients with APRI score ≥1, but after treatment all these 4 patients experienced improvement of liver fibrosis, with all subjects had an APRI score of < 1.

FIB 4 index decreased after HCV/HIV coinfected patients were treated with Sofosbuvir/Daclatasvir achieving SVR 24 as shown by a decrease in median values before and after treatment from 0.94 to 0.81, with a change of 0,13 (95% CI: -0,04 – 0,35). Before treated with Sofosbuvir/Daclatasvir there were 6 (20,7%) subjects who had severe liver fibrosis with FIB-4 index of ≥1,45, meanwhile after treatment with Sofosbuvir/Daclatasvir there were only 1 (3,5%) subject with severe liver fibrosis, 5 remaining patients experienced liver fibrosis improvement with FIB-4 value of < 1,45.

The results of this study were in accordance with previous studies which stated that Hepatitis C treatment that successfully achieves SVR in HCV monoinfected patients or HCV/HIV coinfected patients may decrease liver fibrosis. A study in Switzerland by Bachofner et al reported that SVR might decrease liver fibrosis in HCV monoinfected patients, where liver fibrosis before and 18 months after therapy was calculated using transient elastography (TE), APRI score and Fib-4 index. This study involved 549 patients, where all patients received DAA. Median TE before DAA treatment was 12.65 kPa (IQR 9.45-19.2 kPa), meanwhile 18 months after therapy decreased to 8.55 kPa (IQR 5.93-15.25), with $p < 0.001$. Median FIB-4 index and APRI score also decreased significantly from 2.54 (IQR 1.65-4.43) and 1.10 (IQR 0.65-2.43) to 1.80 (IQR 1.23-2.84, $p < 0.001$) and 0.43 (IQR 0.3-0.79), $p < 0.001$).[35] A study by Chekuri et al which involved 100 HCV patients in

New York in 2016 stated that liver fibrosis decreased after patients achieved SVR 24, with an LS median score decreased from 10.40 kPa (IQR: 7.25-18.60) before treatment to 7.60 kPa (IQR: 5.60-12.38) when SVR 24 with $p < 0.01$.[36]

A study in HCV/HIV coinfected patients by Salmon et al in France, from 98 patients who were treated with combination of peg-interferon and ribavirin or protease inhibitor, 53 (54%) patients achieved SVR. There was a decrease in liver fibrosis at least 30% which was calculated using TE in patients who achieved SVR, which were 51% (95% CI: 39-66). This value was higher compared to patients who did not achieve SVR which was only 21% (95% CI:11-36). Meanwhile, in the second year follow up, 74% (95%CI:61-86) patients achieved SVR experienced decrease in liver fibrosis as much as 30 % compared to 28% (95% CI: 17-24) in patients without SVR.[37] Meanwhile, the study by Mehrez et al in Egypt with a total of study subjects of 50 patients reported that treatment with DAAs in HCV/HIV coinfected patients might decrease liver fibrosis 12 weeks after treatment. APRI score decrease up to 66% while the FIB-4 index decreased to 36.8%.[12]

Before being treated with Sofosbuvir/Daclatasvir, there was 4 HCV/HIV coinfected patients who experienced cirrhosis, marked by APRI score ≥ 1. After sofosbuvir/daclatasvir treatment, all patients experienced improvement in liver fibrosis which was marked by the decrease of APRI score <1. It showed that liver fibrosis in HCV infected patients is reversible. A study on the reversibility of liver cirrhosis have been studied previously. In a meta-analysis study which involved 137 HCV patients who succeeded in achieving SVR after being treated with interferon regiment found regression in liver cirrhosis in 51% sample, whereas the longer the duration between liver histology sample collections, the liver fibrosis decrease was even higher.[38] Data regarding the reversibility of liver cirrhosis in HCV infected patients who were treated with DAAs has not been widely studied as currently liver biopsy examination is rarely performed in HCV infected patients, while liver biopsy is still considered as the gold standard in evaluating reversibility of liver cirrhosis.[39] Pineda et al performed a study to observe the change of liver fibrosis using TE in cirrhosis patients caused by HCV. There were 49 patients with TE value of >12,5 kPa who succeeded to achieve SVR 12 after DAAs treatment. In this study, there was a liver cirrhosis reversibility in 12 patients (24%).[38,39]

Reversibility of liver cirrhosis did not occur in all cirrhosis patients who achieve SVR. In the study performed by Grgurevic et al, it was concluded that cirrhosis reversibility only happens in patients with compensated cirrhosis. HCV eradication in patients with decompensated liver cirrhosis will not stop the development of liver fibrosis.[38] A study performed by Lens et al and Mandrofer et al concluded that administration of DAA treatment in patients with significant portal hypertension did not succeed to decrease portal pressure in majority of patients.[38,40] In patients with decompensated liver cirrhosis which was caused by HCV, it would be better if DAAs was not only given to decrease liver fibrosis but also can be given as antifibrosis drug, although this may need further studies.[38]

This study showed that Sofosbuvir/Daclatasvir treatment can decrease liver fibrosis, which was calculated using APRI score or even FIB-4 index, in HCV/HIV coinfected patients. Evaluation of liver fibrosis in HCV infected patients was an important factor not only to observe the success of treatment but also to determine patient's prognosis.[41,42] The decrease in liver fibrosis is very important as it has been proven to decrease mortality and liver cancer incidence in HCV infected patients.[37,41,43]

In HCV/HIV coinfected patients, there was an increase of hepatocyte apoptosis which cause the activation of stellate cell and increase collagen expression or inflammation mediator. Successful Hepatitis C treatment in HCV/HIV coinfected patients, which was marked by the achievement of SVR, may cause apoptosis of stellate cells and decrease in liver fibrosis.[44-46]

The limitations of this study include: (1) This study did not include data on other factors which may influence liver fibrosis such as the use of other drugs beside ARV and Sofosbuvir/Daclatasvir, the use of alcohol and other disease which may cause liver fibrosis such as metabolic syndrome; (2) There was a lot of study subjects with incomplete data who needs to be excluded, thus may alter the study results; (3) This study did not include HCV genotype data, thus this study may not be applied in all population of HCV/HIV coinfected patients.

CONCLUSION

There was an improvement in the degree of liver fibrosis which was signified by the decrease of APRI score and FIB-4 index in HCV/HIV coinfected patients

in Gastroentero-hepatology Outpatient Clinic in Dr. Hasan Sadikin Hospital Bandung after Sofosbuvir/ Daclatasvir treatment.

REFERENCES

1. Hajarizadeh B, Grebely J, Dore GJ. Epidemiology and natural history of HCV infection. Nat rev Gastroenterol hepatol 2013;10:553-62.
2. Wyles DL, Sulkowski MS, Dieterich D. Management of hepatitis C/HIV coinfection in the era of highly effective hepatitis C virus direct-acting antiviral therapy. Clin infect dis 2016;63:S3-S11.
3. Bruno G, Saracino A, Scudeller L, Fabrizio C, Dell'Acqua R, Milano E, et al. HCV mono-infected and HIV/HCV co-infected individuals treated with direct-acting antivirals: to what extent do they differ? Int J Infect Dis 2017;62:64-71.
4. Sherman KE, Thomas D, Chung RT. Human immunodeficiency virus and liver disease forum 2012. Hepatology 2014;59:307-17.
5. Mastroianni CM, Lichtner M, Mascia C, Zuccala P, Vullo V. Molecular mechanisms of liver fibrosis in HIV/HCV coinfection. Int J Mol Sci 2014;15:9184-208.
6. Kirk G, Mehta S, Astemborski J, Galai N, Washington J, Higgins Yea. HIV, age, and the severity of hepatitis C virus-related liver disease: a cohort study. Ann Intern Med 2013;158:658-66.
7. Rollet-Kurhajec KC, Moodie EE, Walmsley S, Cooper C, Pick N, Klein MB. Hepatic Fibrosis Progression in HIV-Hepatitis C Virus Co-Infection--The Effect of Sex on Risk of Significant Fibrosis Measured by Aspartate-to-Platelet Ratio Index. PloS one 2015;10:e0129868.
8. Sanmartin R, de Felipe E, Tor J, Sanvicens A, Barluenga E, Martinez E. Effect of Liver Fibrosis on Long-Term Mortality in HIV/Hepatitis C Virus-Coinfected Individuals Who are Evaluated to Receive Interferon Therapies in The Highly Active Antiretroviral Therapy Era. AIDS Res Hum Retrov 2012;28:1235-43.
9. Bansal M, Friedman S. Hepatic Fibrogenesis. In: Dooley J, Lok AS, Burroughs AK, Heathcote EJ, eds. Sherlock's Disease of The Liver and Biliary System. 12th ed. West-Sussex: Wiley-Blackwell; 2011.p.94-101.
10. Crane M, Iser D, Lewin S. Human immunodeficiency virus and the liver. World J Hepatol 2012;4:91-8.
11. Dolmazashvili E, Abutidze A, Chkhartishvili N, Karchava M, Sharvadze L, Tsertsvadze T. Regression of liver fibrosis over a 24-week period after completing direct-acting antiviral therapy in patients with chronic hepatitis C receiving care within the national hepatitis C elimination program in Georgia: results of hepatology clinic HEPA experience. Eur J Gastroenterol Hepatol 2017;29:1223-30.
12. Mehrez MI, Saleh M, Fareid A. Fibrosis Regression After Treatment with DAAs. Medcrave 2017;7:4.
13. Monje-Agudo P, Castro-Iglesias A, Rivero-Juarez A, Martinez-Marcos F, Ortega-Gonzalez E, Real LM, et al. Impact of HIV infection on sustained virological response to treatment against hepatitis C virus with pegylated interferon plus ribavirin. Eur J Clin Microbiol Infect Dis 2015;34:1929-36.
14. Flisiak R, Pogorzelska J, Flisiak-Jackiewicz M. Hepatitis C: efficacy and safety in real life. Liver Int 2017;37:26-32.
15. Shadish, Cook, Cambell. Experimental and Quasi Experimental Designs for Generalized causal inferference. Boston: Houghton Mifflin;2002.
16. Harris AD, McGregor JC, Perencevich EN, Furuno JP, Zhu J, Peterson DE, et al. The use and interpretation of quasi-experimental studies in medical informatics. JAMIA 2006;13:16-23.
17. Dahlan S. Besar Sampel Dalam Penelitian Kedokteran Dan Kesehatan. Komparatif Numerik Berpasangan Pengukuran Berulang Dua Kali Pengukuran. Jakarta: Epidemiologi Indonesia; 2016.p.221-8.
18. Shiffman ML, Sterling RK, Contos M, Hubbard S, Long A, Luketic VA, et al. Long term changes in liver histology following treatment of chronic hepatitis C virus. Ann Hepatol 2014;13:340-9.
19. Dahlan S. Statsitik Untuk Kedokteran Dan Kesehatan. Jakarta: Epidemiologi Indonesia;2016.p.47.
20. Wisaksana R, Sumantri R, Indrati AR, Zwitser A, Jusuf H, de Mast Q. Anemia and Iron Homeostasis in A Cohort of HIV-Infected Patients in Indonesia. BMC Infect Dis 2011;11:213.
21. Chen M, Wong WW, Law MG, Kiertiburanakul S, Yunihastuti E, Merati TP, et al. Hepatitis B and C Co-Infection in HIV Patients from the TREAT Asia HIV Observational Database: Analysis of Risk Factors and Survival. PloS one 2016;11:e0150512.
22. Nunes D, Fleming C, Offner G, Craven D, Fix O, Heeren Tea. Noninvasive Markers of Liver Fibrosis are Highly Predictive of Liver-Related Death in a Cohort of HCV-infected Individuals With or Without HIV Infection. Am J Gastroenterol 2010;105:1346-53.
23. Sanvisens A, Fuster D, Serra I, Tor J, Tural C, Rey-Joly C, et al. Estimated liver fibrosis and its impact on all-cause mortality of HCV-monoinfected and HCV/HIV-coinfected drug users. Curr HIV Res 2011;9:256-62.
24. Dusheiko G. Hepatitis C. In: Dooley J, Lok A, Burroughs A, Heathcote E, eds. Sherlock's Disease of The Liver and Biliary System. 12th ed. United Kingdom: Wiley-Blackwell Publishing; 2011.p.406-24.
25. Sahin E, Colla S, Liesa M, Moslehi J, Muller FL, Guo M, et al. Telomere dysfunction induces metabolic and mitochondrial compromise. Nature 2011;470:359-65.
26. Wyles DL, Ruane PJ, Sulkowski MS, Dieterich D, Luetkemeyer A, Morgan TR, et al. Daclatasvir plus Sofosbuvir for HCV in Patients Coinfected with HIV-1. N Engl J Med 2015;373:714-25.
27. Hasan I, Gani R, Sulaiman A, Lesmana C, Kurniawan J, Jasirwan C, et al. Konsensus Nasional Penatalaksanaan Hepatitis C. PPHI. 2017.
28. Chen J, Florian J, Carter W, Fleischer RD, Hammerstrom TS, Jadhav PR, et al. Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies. Gastroenterology 2013;144:1450-5 e2.
29. Sogni P, Gilbert C, Lacombe K, Piroth L, Rosenthal E, Miailhes P, et al. All-oral Direct-acting Antiviral Regimens in HIV/Hepatitis C Virus-coinfected Patients With Cirrhosis Are Efficient and Safe: Real-life Results From the Prospective ANRS CO13-HEPAVIH Cohort. Clin Infect Dis 2016;63:763-70.
30. Labargo P, Fernandez-Montero J, Mendoza Cd, barrreiro P, Pinnila J, Soriano V. Liver fibrosis progression despite HCV Cure with antiviral therapu in HIV-HCV-Coinfected patients. Int Med Press 2016;10:x.
31. Khan ST, McGuinty M, Corsi DJ, Cooper CL. Liver enzyme normalization predicts success of Hepatitis C oral direct-acting antiviral treatment. Clinical and investigative medicine Medecine clinique et experimentale 2017;40:E73-E80.

32. Kee KM, Wang JH, Hung CH, Chen CH, Lee CM, Lu SN. Improvement of thrombocytopenia in hepatitis C-related advanced fibrosis patients after sustained virological response. Dig Dis Sci 2013;58:556-61.
33. Kan T, Hashimoto S, Kawabe N, Nakano T, Nakaoka K, Yoshioka K. Increase in Albumin by Daclatasvir/asunaprevir Therapy is Correlated with Decrease in Aspartate Transaminase. J Transl Med 2017;5:148-54.
34. Ni Z, Yuan Y, Wang Q, Cao L, Che X, Zhang M, et al. Time-averaged albumin predicts the long-term prognosis of IgA nephropathy patients who achieved remission. J Transl Med 2014;12:194.
35. Bachofner JA, Valli PV, Kroger A, Bergamin I, Kunzler P, Baserga A, et al. Direct antiviral agent treatment of chronic hepatitis C results in rapid regression of transient elastography and fibrosis markers fibrosis-4 score and aspartate aminotransferase-platelet ratio index. Liver Int 2017;37:369-76.
36. Chekuri S, Nickerson J, Bichoupan K, Sefcik R, Doobay K, Chang S, et al. Liver Stiffness Decreases Rapidly in Response to Successful Hepatitis C Treatment and Then Plateaus. PloS one 2016;11:e0159413.
37. Cohort ACH. Regression of liver stiffness after sustained hepatitis C virus (HCV) virological responses among HIV/HCV-coinfected patients. Aids 2015;29:1821-30.
38. Grgurevic I, Bozin T, Madir A. Hepatitis C is now curable, but what happens with cirrhosis and portal hypertension afterwards? Clinical and experimental hepatology 2017;3:181-6.
39. D'Ambrosio R, Aghemo A, Fraquelli M, Rumi MG, Donato MF, Paradis V, et al. The diagnostic accuracy of Fibroscan for cirrhosis is influenced by liver morphometry in HCV patients with a sustained virological response. J hepatol 2013;59:251-6.
40. Mandorfer M, Kozbial K, Schwabl P, Freissmuth C, Schwarzer R, Stern R, et al. Sustained virologic response to interferon-free therapies ameliorates HCV-induced portal hypertension. J hepatol 2016;65:692-9.
41. Carmona I, Cordero P, Ampuero J, Rojas A, Romero-Gomez M. Role of assessing liver fibrosis in management of chronic hepatitis C virus infection. Clinical microbiology and infection 2016;22:839-45.
42. Massard J, Ratziu V, Thabut D, Moussalli J, Lebray P, Benhamou Y, et al. Natural history and predictors of disease severity in chronic hepatitis C. J hepatol 2006;44:S19-24.
43. Cardoso AC, Moucari R, Figueiredo-Mendes C, Ripault MP, Giuily N, Castelnau C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. J hepatol 2010;52:652-7.
44. Casado JL, Quereda C, Moreno A, Perez-Elias MJ, Marti-Belda P, Moreno S. Regression of liver fibrosis is progressive after sustained virological response to HCV therapy in patients with hepatitis C and HIV coinfection. J Viral Hepat 2013;20:829-37.
45. Barreiro P, Labarga P, Martin-Carbonero L, Amor A, Ruiz-Sancho A, Castellares C, et al. Sustained virological response following HCV therapy is associated with non-progression of liver fibrosis in HCV/HIV-coinfected patients. Antiviral therapy 2006;11:869-77.
46. Chakraborty JB, Oakley F, Walsh MJ. Mechanisms and biomarkers of apoptosis in liver disease and fibrosis. Int J Hepatol 2012;2012:648915.