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Research Article

ASSOCIATION BETWEEN GLOMERULAR FILTRATION RATE AND DIRECT-ACTING ANTIVIRAL REGIMENT IN CHRONIC HEPATITIS C: A RETROSPECTIVE COHORT STUDY

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ABSTRACT

Treatment of hepatitis C virus (HCV) infection is currently developing, but some antiviral agents are reported to cause kidney dysfunction. Currently, direct-acting antivirals (DAA) are the best choice in the management of HCV infection with high efficacy, minimal side effects and better tolerability. This study was conducted to evaluate the glomerular filtration rate (GFR) given DAA regiment outcome in hepatitis C patients. An observational analytic study, with a prospective cohort design, was conducted at Wahidin Sudirohusodo Hospital. Subjects included were patients diagnosed with HCV infection and treated with DAA. Patients with hepatitis B or human immunodeficiency virus co-infection or have chronic kidney disease were excluded. Serum creatinine was evaluated before and after observational period; 12 weeks in non-cirrhosis and 24 weeks in cirrhosis patients. Independent t-test, Paired t-test, and Chi-square were used for statistical analysis of the data. A total of 50 subjects were evaluated, 25 subjects (50 %) included to the sofosbuvir-simeprevir regiment group, 22 subjects (44 %) in sofosbuvir-daclatasvir regiment group and 3 subjects (6 %) in sofosbuvir-ribavirin regiment group. There is no association between 12 weeks or 24 weeks of treatment period with GFR in pre- and post-DAA treatment (p-value > 0.05). There is no association between the type of DAA combination regiment with GFR in pre- and post-DAA treatment (p-value > 0.05). There is no association between DAA characteristic based on the duration of treatment and regiment of DAA with glomerular filtration rate in chronic hepatitis C patients.

Keywords: direct-acting antiviral, hepatitis C, glomerular filtration rate.

INTRODUCTION

It is estimated that around 130-170 million people are infected with hepatitis C virus (HCV) worldwide or 2.35 % of the total world population. WHO states that there are 3-4 million new cases of hepatitis C each year. Increased incidence of HCV infection will further increase morbidity and mortality.[1]

Eradication of HCV is expected to reduce morbidity and mortality in patients. However, some antivirals have been reported to cause kidney dysfunction and organ damage.[2] Currently, direct-acting antivirals (DAA) are the best choice in the management of HCV infection, with high efficacy, minimal side effects, and better tolerability. It is also can be administered to HCV patients with chronic kidney disease.[3]

In Indonesia, currently there were no studies that describe the effect of DAA regiment on glomerular filtration rate, therefore this study was conducted to determine the effect of DAA regiment on glomerular filtration rate in hepatitis C patients.

MATERIAL AND METHODS

This is an observational analytic study, with a prospective cohort design. This study was conducted at Wahidin Sudirohusodo Hospital Makassar from January 2017 to July 2019. Subjects included in this study were hepatitis C patients who received DAA regiments. Patients with hepatitis B or human immunodeficiency virus co-infection or have chronic kidney disease or on dialysis were excluded.

Subjects were recruited with consecutive sampling method, where patients who met the inclusion criteria in this study were included until the certain number of research sample requirement was met. Creatinine serum level was measured before and after DAA therapy and GFR was calculated using CKDEPI (Chronic Kidney Disease Epidemiology Collaboration Equation) formula. The period of treatment was 12 weeks in non-cirrhosis and 24 weeks in cirrhosis patients.

Results obtained were analyzed through computer software using the Statistical Package for Social Science (SPSS) version 22. The statistical analysis conducted was descriptive statistical calculations and frequency distribution as well as Paired t-tests, Independent t-test, and Chi-square. The test results considered significant with p-value < 0.05.

The study has been approved and acknowledged by Ethical and Medical Committee of Hasanuddin University.

RESULTS

A total of 50 subjects met the inclusion criteria. 37 of the participants were male (74 %), 22 participants aged less than 40 years old (44 %), 25 participants treated with sofosbuvir-simeprevir (50 %), 38 subjects had no hypertension (76 %) and 29 subjects already had cirrhosis (29 %) (Table 1).

Table 1: Characteristics of research subjects

Variable		n	%
Gender	Male	37	74.0
	Female	13	26.0
Age	< 40 years old	22	44.0
	40-59 years old	20	40.0
	≥ 60 years old	8	16.0
Therapeutical Regiments	Sofosbuvir-Simeprevir	25	50.0
	Sofosbuvir-Daclatasvir	22	44.0
	Sofosbuvir-Ribavirin	3	6.0
Hypertension	Present Absent	12 38	24.0 76.0
Cirrhosis	Present Absent	29 21	58.0 42.0

Subjects who received 12-weeks of DAA had increased post-treatment GFR level compared to pre-treatment ones, but the association was not significant ($p > 0.05$). Subjects who received 24-weeks DAA had a decrease in post-treatment GFR level but the association was also not significant ($p > 0.05$) (Table 2).

Table 2: Association between treatment period and GFR pre- and post-DAA

Duration of Therapy	Variable	n	Mean	SD	p
12 weeks	GFR Pre	29	104.3	20.0	0.623
	GFR Post	29	106.3	32.2	
24 weeks	GFR Pre	21	102.9	19.4	0.321
	GFR Post	21	97.8	31.1	

In 12-weeks of DAA treatment group, sofosbuvir-simeprevir regiment caused a decrease in pre and post-treatment GFR meanwhile sofosbuvir-daclatasvir increased GFR, but the association in both regiment combinations were not significant ($p > 0.05$) (Table 3). In 24-weeks of DAA treatment group, the combination of sofosbuvir-simeprevir decreased pre- and post-treatment GFR, along with sofosbuvirdaclatasvir, meanwhile sofosbuvir-ribavirin associated with increased GFR. Unfortunately, the association in all regiment combinations were not significant ($p > 0.05$). (Table 3)

Table 3: Comparison of DAA combination regiments effect on pre- and post-treatment GFR

Duration of therapy	Regiment combination	GFR	N	mean	SD	p
12 weeks	Sofosbuvir Simeprevir	Pre	15	101.9	16.6	0.783
		Post	15	100.1	33.2	
	Sofosbuvir Daclatasvir	Pre	13	108.4	23.6	0.177
		Post	13	114.1	31.9	
	Sofosbuvir Ribavirin	Pre	1	88.0	.	-
		Post	1	98.0	.	
24 weeks	Sofosbuvir Simeprevir	Pre	10	103.3	17.1	0.469
		Post	10	96.5	38.0	
	Sofosbuvir Daclatasvir	Pre	9	102.3	22.0	0.515
		Post	9	97.8	27.1	
	Sofosbuvir Ribavirin	Pre	2	103.5	31.8	0.963
		Post	2	104.0	19.8	

DISCUSSION

This study included 50 subjects aged between 29-80 years with a mean of 45.5 ± 14.1 years. The prevalence of male with HCV infection is higher, at 74.0 % compared to female, at 26.0 %. In line with research by Bergman et al, it was found that most patients with hepatitis C were male (71.7 %) with average age of 47-54 years ($p < 0.0001$).[4]

The purpose of giving DAA for 12 weeks is to eradicate the hepatitis C virus and prevent complications.[5] In Indonesia, genotype 1 virus is the most found.[5-7] According to the National Consensus on Hepatitis C Management in Indonesia, first-line therapy for genotype 1 HCV infection included a combination of sofosbuvir-simeprevir and sofosbuvir-daclatasvir.[2] In this study, we administered sofosbuvir-simeprevir to 25 subjects (50.0 %) and sofosbuvir-daclatasvir in 22 subjects (44.0 %).

The DAA regimen is given for 12 weeks in non-cirrhosis patients, while the cirrhosis patient is given the DAA regimen for 24 weeks. The presence of cirrhosis - especially the type of decomposition is a risk factor for decreased kidney function and creatinine clearance within 1-2 weeks or decreased GFR with an increase in serum creatinine.[8] Duration of drug administration will enhance the toxic effects of the drug on kidneys.[9] Therefore, in Table 2, 24-week DAA administration in cirrhosis subjects decreased GFR and 12-week DAA provided improvement in post-therapy GFR, but it was not statistically significant ($p > 0.05$).

Sofosbuvir and daclatasvir regimens, as well as sofosbuvir and ribavirin given for 12 weeks showed to improved GFR. This is because basically, sofosbuvir-based regimens are safe to administered and do not require dosage adjustments even in

patients with chronic kidney disease (GFR ≤ 30 ml/min/1,73 m^2).[10] Research conducted by Chin-chin Kao *et al*., reported that the group without renal impairment and early CKD (GFR ≥ 60 ml/min/1,73 m^2) had a lower risk of kidney dysfunction compared to the advanced CKD group (GFR < 60 ml/min/1,73 m^2) after DAA administration.[11] And a study from Taiwan by Hsu *et al*., stated that in HCV-infected patients who was successfully treated, there was an improvement in GFR, thereby reducing the risk of end-stage renal disease by 84 %.[12]

CONCLUSION

There is no significant effect of the administration of direct-acting antiviral regimens on the improvement of glomerular filtration rate in hepatitis C patients.

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