The Efficacy of Administering Elbasvir/Grazoprevir in Chronic HCV Patients with End-Stage Renal Disease

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ABSTRACT

Introduction: *Managing chronic hepatitis C (HCV) in terminal chronic kidney disease (CKD) patients is considered a significant challenge to the health sector. Although elbasvir and grazoprevir are combinedly used as a direct-acting antiviral (DAA) medication for treating HCV with kidney complications, research is scarce on the efficacy of the combination among individuals having end-stage renal disease (ESRD). Therefore, this research delineated the efficacy of elbasvir/grazoprevir combination in treating HCV among individuals with ESRD.*

Method: *The methodology used an analytic observational design with a cross-sectional approach. To assess the efficacy of elbasvir/grazoprevir combination therapy in treating HCV patients with ESRD, the sustained virological response in 12 weeks and renal function were measured. Data were retrieved from the clinical records at the Hepatology Outpatient Clinic of RSUD Dr. Saiful Anwar from 1 January 2021 to 31 December 2022. Statistical analysis was carried out with SPSS software, with a significant level of $p<0.05$ and a 95% confidence interval.*

Results: *Among 52 participants, the majority achieved an SVR12 rate of 94.23% and the creatinine levels significantly increased from 122 ± 40 to 133.05 ± 36.12 mg/dl ($p=0.032$). However, urea levels showed no significant difference, from 12 ± 3 to 12.2 ± 3.6 mg/dl ($p=0.446$).*

Conclusion: *Based on the results, elbasvir and grazoprevir were found to be an efficacious therapy for HCV treatment in individuals with ESRD.*

Keywords: *efficacy, elbasvir/grazoprevir, HCV, ESRD*

ABSTRAK

Latar Belakang: *Mengelola hepatitis C (HCV) pada individu dengan gagal ginjal terminal masih merupakan kesulitan dalam bidang klinis yang signifikan. Kombinasi elbasvir dan grazoprevir merupakan obat direct-acting antiviral (DAA) yang bermanfaat untuk mengobati pasien HCV dengan komplikasi ginjal. Studi mengenai efikasi elbasvir/grazoprevir pada pasien dengan HCV dan penyakit ginjal kronis stadium akhir masih sedikit. Studi ini berupaya untuk menggambarkan efikasi elbasvir/grazoprevir dalam mengobati HCV di antara individu dengan penyakit ginjal kronis stadium akhir .*

Metode: *Studi ini mengaplikasikan desain observasional analitik dan pendekatan studi cross-sectional. Studi ini ingin menilai efikasi elbasvir/grazoprevir dalam mengobati pasien HCV dengan penyakit ginjal kronis stadium*

akhir dengan mengevaluasi SVR12 serta fungsi ginjal. Data berdasarkan rekam medis penderita hepatitis C kronik yang dirawat di Klinik Rawat Jalan Hepatologi RSUP Dr. Saiful Anwar antara tanggal 1 Januari 2021 sampai 31 Desember 2022. Analisis statistik menggunakan software SPSS, dengan signifikansi ditetapkan pada p<0,05 serta interval kepercayaan 95%.

***Hasil:** Studi ini melibatkan lima puluh dua partisipan. Mayoritas yang diobati dengan elbasvir/grazoprevir mencapai tingkat SVR12 sebesar 94,23%. Terdapat peningkatan yang signifikan pada kadar kreatinin 122 ± 40-133,05 ± 36,12 mg/dl (p=0,032). Namun urea tidak menunjukkan perbedaan bermakna, yaitu 12 ± 3-12,2 ± 3,6 mg/dl (p=0,446).*

***Kesimpulan:** Kombinasi elbasvir/ grazoprevir menunjukkan keefektifan dalam penanganan hepatitis C kronik pada individu dengan penyakit ginjal kronis stadium akhir.*

Kata Kunci: efikasi, elbasvir/grazoprevir, HCV, PGK stadium akhir

INTRODUCTION

Chronic HCV infection is a significant factor in the cirrhosis and liver malignancy development. Approximately 1% of the global population is estimated to have HCV, with 71 million active cases, predominantly in Asian countries such as Indonesia, India, Pakistan, and China.[1] In Indonesia, samples with positive anti-HCV prevalence was 1% with most cases found in elderly aged 60 years and above. A national surveillance project (Riskesdas) and Indonesian Red Cross (IRC) reported an estimated 1.284.000 people with HCV infection in 2014.[2]

HCV infection might predispose individuals to both acute or chronic kidney impairment due to several factors, namely glomerular immune complex deposition, direct viral invasion, manifestations of renal complications, and drug nephrotoxicity. Therapy with conventional interferon/ribavirin protocol, in which both drugs were mainly excreted in urine, remains a clinical concern due to the low sustained virologic response (SVR) rate with limited tolerability attributed to the adverse effects. DAA agents have revolutionized HCV therapy in ESRD patients, ensuring efficacy and safety with no immunostimulatory effect that might cause problems in the kidney.[3]

Elbasvir/grazoprevir is an FDA-approved fixed-dose DAA therapy for chronic HCV genotypes (GTs) [1] and [4] in adults. One tablet contains [50] mg elbasvir and [100] mg grazoprevir to be consumed once per day. This combination is safe for patients having renal impairment with no dosage adjustments required. AASLD/IDSA guidelines also suggest [12] weeks elbasvir/grazoprevir therapy for patients infected by HCV GT [1]a, [1]b, or [4] with ESRD (creatinine clearance <[30] ml/min).[4]

To this date, studies regarding the efficacy of elbasvir/grazoprevir in Indonesian HCV patients with ESRD are limited. Further and more detailed study is needed to explore more about the efficacy of elbasvir and grazoprevir combination in HCV patients with ESRD. This study aimed to evaluated the safety and efficacy of elbasvir/grazoprevir therapy in patients with hepatitis C with ESRD.

METHOD

An observational analytical design was used with a cross-sectional method in evaluating the elbasvir/grazoprevir combination impact on HCV therapy among individuals with ESRD, focusing on parameters such as SVR12 and renal function.

This research used medical records of HCV patients with ESRD and regular hemodialysis history administered elbasvir/grazoprevir combination between January 1, 2021, and December 31, 2022, at the Hepatology Outpatient Clinic of RSUD Dr. Saiful Anwar, Malang. The majority of participants were aged 25-60 years with 31 men and 21 women. The inclusion criteria were outpatients confirmed to have hepatitis C with ESRD through laboratory examination and receiving hemodialysis therapy, hepatitis C patients with ESRD who got elbasvir/grazoprevir therapy for 12 weeks, patients aged > 17 years, had complete medical records including name, medical record number, gender, age, as well as viral load, urea, and creatinine levels at the start and 12 months after completion of therapy. Additionally, participants should not have any other diagnosed kidney diseases, such as trauma, kidney stones, tumors, or congenital conditions. The exclusion criteria were age < 17 years, hepatitis C patients with ESRD who did not complete elbasvir/grazoprevir therapy for 12 weeks, did not have complete medical records, or diagnosed other kidney diseases such as trauma, kidney stones, tumors, and congenital.

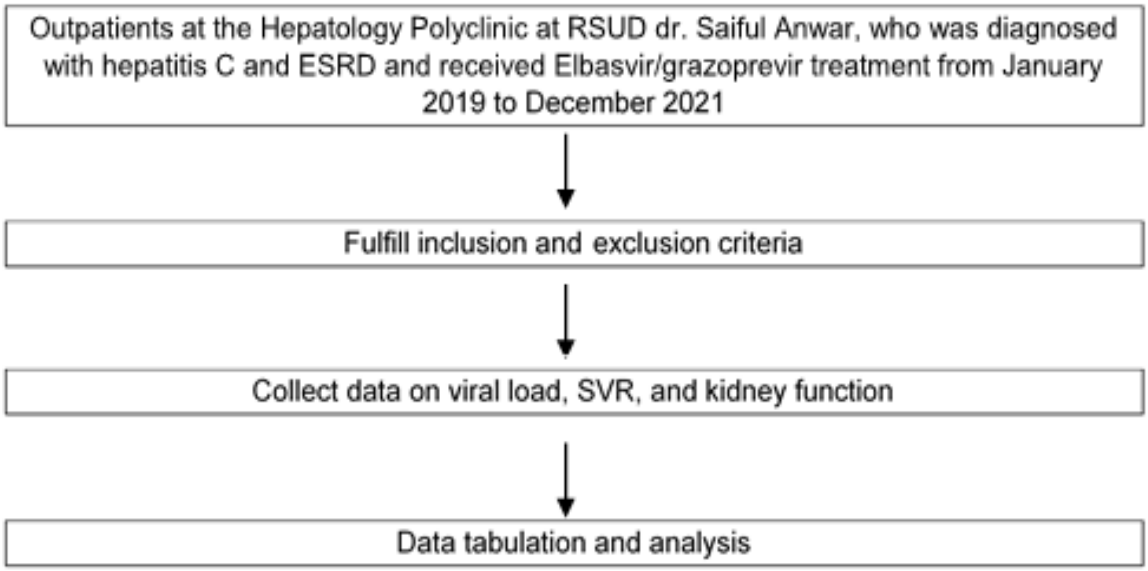

Figure 1. Research flow

Considering this research used medical records, written informed consent was waived and data were recorded anonymously to ensure confidentiality. The protocol of the research had been ethically accepted by the Health Research Ethic Committee, Medicine Faculty, Universitas Brawijaya (No. 78/EC/KEPK/03/2021).

Comparison between variables was conducted applying the chi-square test with a significant level at $p<0.05$ and a 95% confidence interval. SVR12 and kidney function data before and after the therapy were presented as numerical values. The comparison was performed using the paired t-test, while the statistical analysis applied the Wilcoxon test. Then, the statistical analysis applied Statistical Product and Service Solution (SPSS) software.

Definition of response

Chronic hepatitis C infection is disease caused by HCV which is diagnosed based on an ELISA or CLIA examination with a positive anti-HCV value and followed by an HVC RNA examination. Meanwhile, end-stage renal disease (ESRD) is characterized by increased urea and creatinine, with a GFR <15 that persists for three months necessitating routine hemodialysis as renal replacement therapy. Total Viral Load refers to the total HCV in a person's blood at the start and 12 weeks after completing elbasvir/grazoprevir therapy which was obtained applying the PCR method and included in the medical record.

Sustained virologic response 12 (SVR12), is the number of undetectable HCV RNA levels 12 weeks after completion of elbasvir/grazoprevir therapy. Urea levels refer to the measurements taken at the start and 12 weeks after completion of therapy. It was measured using an automated chemistry analyzer and included in the medical record. Creatinine levels refer to measurements taken at the start of therapy and 12 weeks after completion.

RESULT

Based on Table 1, the participants' characteristics are dominated by males. The average age was 52.21 years, with a significant proportion falling within the 51-60 age range. Hepatitis C history was reported in five patients, while three had compensated cirrhosis. A total of 69.2% showed HCV RNA viral load <800,000 IU/mL.

This research examined the SVR12 rate among HCV-infected patients with ESRD who got elbasvir/grazoprevir combination therapy. SVR12 refers to undetectable viral load of HCV RNA 12 weeks after completing therapy. As shown in Figure 1, most of patients achieved an SVR12 rate of 94.23, while the non-SVR rate was 5.77%.

An analysis was conducted to determine factors related to achieving SVR12 and the results are described in Table 2. Table 2 indicates the comparison of patient characteristics with SVR. Several characteristics including gender (p=0.142), age (p=0.635), previous hepatitis C infection (p=0.561), and HCV RNA at

Table 1. Characteristics of Participants

Parameters	Mean±SD	n	(%)
Gender			
Male		31	59,6
Female		21	40,4
Age			
25-50 Years		16	30,8
51-60 Years		25	48,1
>60 Years		11	21,2
Previous Hepatitis C Infection			
Present		5	9,6
Absent		47	90,4
Liver Cirrhosis			
Present		3	5,8
Absent		49	94,2
HCV RNA			
>800.000 IU/mL		16	30,77
<800.000 IU/mL		36	69,23
Ureum			
Pre-therapy (mg/dl)	122±40		
Post-therapy (mg/dl)	133,05±36,12		
Creatinin			
Pre-therapy (mg/dl)	12±3		
Post-therapy (mg/dl)	12,2±3,6		

HCV: hepatitis C virus; HIV: human immunodeficiency virus; RNA: ribonucleic acid

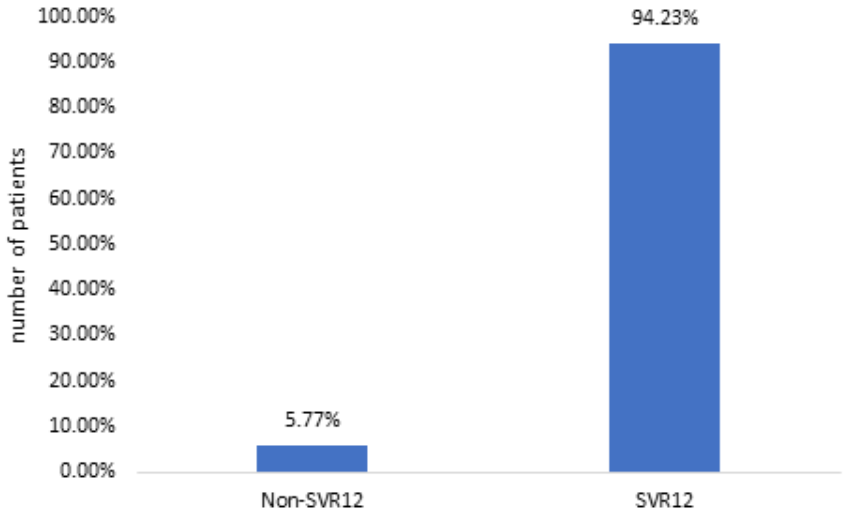

Figure 2. Percentage of SVR12 and non-SVR12 in 12th week after completing therapy

early therapy (p=0.165) were not related to SVR values. Meanwhile, cirrhosis complications (p=0.035) were significantly related. Figures 3 and 4 show the variances in creatinine as well as urea levels pre- and post-therapy. Specifically, creatinine content rose from an initial value of 122 ± 40 to 133.05 ± 36.12 mg/dl. Due to the abnormal data distribution of creatinine levels, the Wilcoxon test was used, showing a significant increase (p=0.032; p<0.05). Urea levels also rised from 12 ± 3 to 12.2 ± 3.6 mg/dl, with normal data distribution. Therefore, the paired t-test was used, showing insignificant differences pre- and post-therapy (p=0.446; p>0.05).

Table 2. Comparison characteristics of patients based on virologic response

Characteristics	SVR 12	Non-SVR12	p-value
Gender			0,142
Male	28	3	
Female	21	0	
Age			0,635
25-50 Years	15	1	
51-60 Years	23	2	
>60 Years	11	0	
Previous Hepatitis C Infection			0,561
Present	5	0	
Absent	44	3	
Liver Cirrhosis			0,035*
Present	47	2	
Absent	2	1	
HCV RNA			0,165
>800.000 IU/ml	14	2	
<800.000 IU/ml	35	1	

SVR : sustained virologic response; *Showed statistically significant, with p<0.05

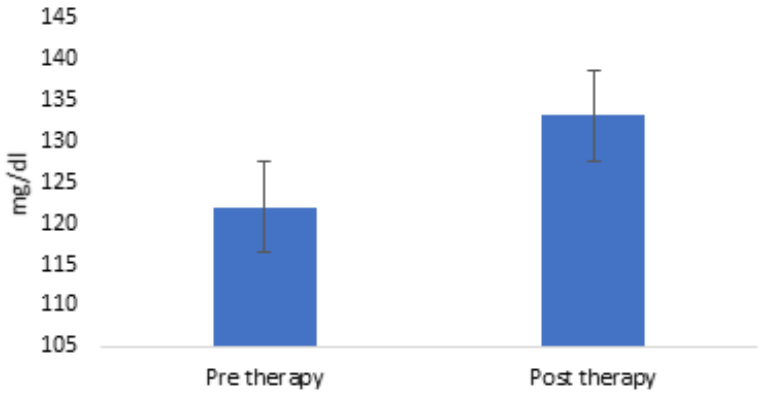

Figure 3. Urea levels pre- and post-therapy (p=0.446)

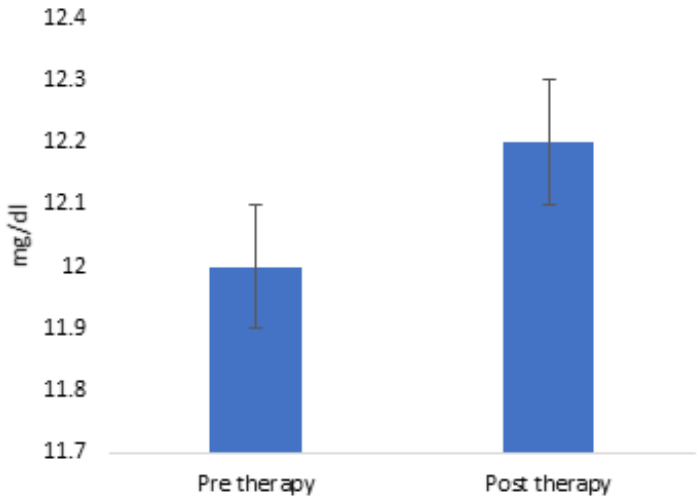

Figure 4. Creatinin levels pre- and post-therapy (p=0.032)

DISCUSSION

Elbasvir and grazoprevir are DAA drugs widely used since 2016 for treating chronic HCV infections, specifically genotype 1 or 4. Generally, elbasvir works by inhibiting NS5A, a nonstructural protein of HCV, while grazoprevir functions by inhibiting NS3/4A protease. Both NS5A and NS3/4A are responsible for RNA replication and viral assembly.[5] SVR12 (sustained virological response in 12 weeks) is an indicator showing undetectable viral load of HCV RNA 12 weeks after completing therapy.6 This research showed that patients receiving elbasvir and grazoprevir combination therapy achieved 94.23% SVR12. Similar results were stated by an analysis of Asian participants with HCV genotype 1 or 4 infection from 15 countries, in which SVR12 was achieved by 96.9%.[7]

A total of 5.76% total patients did not achieve SVR in this research. Genotype and resistance-associated substitutions (RAS) are important in predicting SVR.[8] Other influential factors of therapy efficacy include viral load, viral response, host characteristics, IL-28B polymorphism, and extent of liver cirrhosis.[9] IL-28B polymorphism is mainly used to predict PEG-IFN and ribavirin treatment response in patients infected with HCV genotype [1]. A study showed that patients with IL-28B gene CC genotype tend to achieve spontaneous HCV viral clearance than progression to chronic HCV infection.[10] Diabetes mellitus and hypertension comorbidities in hepatitis C patients receiving routine hemodialysis also influenced SVR. Patients with comorbidities have a higher tendency to experience non-SVR compared to those without. This is attributed to chronic inflammation in comorbidities which reduces the effectiveness of antiviral drugs.[11] Common adverse events reported from patients receiving elbasvir/grazoprevir therapy include itching, ALT elevation, dyspepsia, fatigue, epigastric pain, and nausea.8 A cohort research showed that the most common causes of non-SVR were incomplete therapy and compliance failure.[12]

In this research, SVR12 were achieved in 97.2% (35 of 36) and 87.5% (14 of 16) in patients with baseline HCV RNA of <800,000 IU/mL and >800,000 IU/mL respectively. To note, there was no significant correlation found between SVR12 and HCV RNA. Our analysis to determine factors related to SVR showed that only cirrhosis complication were significantly related to SVR values. Patients with HCV infection and cirrhosis complication were more challenging to treat due to their low response rate and low tolerability to interferon-based regimens. Currently, a 12-week DAA regimen had been approved for treating patients with HCV genotype 1 and compensated cirrhosis. However, cirrhotic patients who might have failed a prior DAA treatment will have to undergo a 24-week regimen or add ribavirin to the regimen in order to achieve higher SVR12. [13]

This research found an insignificant increase in the urea level, while a significant rise was analyzed in the creatinine level after elbasvir/grazoprevir combination therapy. Several factors might influence our different results from other studies, including the time frame differences of hemodialysis in each patient, lesser sample sizes, and uncalculated GFR values. Previous studies on elbasvir/grazoprevir safety administration suggested that this drug combination was rarely excreted from kidneys and safe for patients having any stage of chronic kidney disease (CKD) with no dosage adjustments needed.[14] Furthermore, the research found that elbasvir/grazoprevir did not significantly decrease eGFR in Japanese genotype 1b hepatitis C patients with CKD comorbidity.[15] Another research on phase II/III clinical trials of elbasvir/grazoprevir therapy in hepatitis C infection and pre-existing stage 3 CKD patients showed no decline in eGFR compared to baseline both at the end and 12 weeks after therapy.[16]

This research had several limitations, firstly, it lacked information on patients' sexual history, substance abuse, history of other comorbidities (diabetes mellitus), BMI (obese condition), time span between HCV diagnosis and hemodialysis, and extent of liver cirrhosis. Secondly, the HCV genotypes and IL28B variations were not specified. Thirdly, the time lapse from the final hemodialysis session to renal function assessment was not examined, potentially introducing measurement bias, and GFR was not calculated as in previous studies.

CONCLUSION

In conclusion, the combination of elbasvir/grazoprevir therapy has great efficacy in treating HCV infection in ESRD patients. Patients receiving this therapy achieved 94.23% SVR12. Although elbasvir/grazoprevir led to an elevation in creatinine levels, it did not impact urea levels.

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