

Sofosbuvir/Daclatasvir versus Grazoprevir/Elbasvir in Patients with Chronic Hepatitis C on Haemodialysis: A Multicentre, Single-Blind, Randomised Controlled Trial

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ABSTRACT

Background: Patients with chronic kidney disease undergoing hemodialysis are at risk of hepatitis C virus exposure due to nosocomial transmission and the duration of hemodialysis. The treatment for hepatitis C in patients with chronic kidney disease undergoing hemodialysis is oral direct-acting antiviral (DAA) therapy, which works directly as an antiviral. Currently, the DAA considered safe for use in patients with chronic kidney disease is grazoprevir/elbasvir. However, this DAA is expensive and effective in patients with genotypes 1 and 4. Recent studies have shown that sofosbuvir-based regimens are safe. Therefore, this study aimed to compare the efficacy and safety of sofosbuvir/daclatasvir with grazoprevir/elbasvir in patients with chronic hepatitis C undergoing hemodialysis. **Methods:** We conducted a multicenter, single-blind, randomized clinical trial that included 120 treatment-naïve, HCV-infected hemodialysis patients. We randomized only participants with fibrosis < F4. Patients with cirrhosis (F4) were assigned to sofosbuvir/daclatasvir per guideline-based contraindications for grazoprevir/elbasvir. Participants received sofosbuvir/daclatasvir or grazoprevir/elbasvir. The primary endpoints were sustained virologic response at week 12 (SVR12) and treatment-related adverse events. Statistical comparisons were conducted using the Mann–Whitney U test for continuous variables and the chi-square test for categorical variables. **Results:** 120 patients completed the study, with no dropouts or missing SVR12 data. All patients (100%) achieved SVR12 in both treatment groups. Sofosbuvir/daclatasvir and grazoprevir/elbasvir achieved 100% SVR at 12 weeks, with good safety and no adverse events in 98.3% of patients. **Conclusion:** Both sofosbuvir/daclatasvir and grazoprevir/elbasvir are highly effective and safe for treating hepatitis C in patients undergoing hemodialysis.

Sofosbuvir/daclatasvir offers broader applicability across all fibrosis stages and genotypes, with substantially lower treatment costs.

Keywords: Hepatitis C; chronic kidney disease; hemodialysis, sofosbuvir/daclatasvir, grazoprevir/elbasvir.

INTRODUCTION

Hepatitis C remains a global health problem. Worldwide, 58 million adults are living with hepatitis C infection, with 1.5 million new infections occurring each year. The World Health Organization (WHO) states that 400,000 people die from hepatitis C annually due to the progression of the infection from acute to chronic stages, leading to cirrhosis and hepatocellular carcinoma.¹ In Indonesia, the prevalence of reactive anti-HCV is 1.01% or about 2.7 million people.²

Chronic kidney disease (CKD) also contributes to global health problems. Global estimates found the prevalence of CKD to be 13.4%.³ In Indonesia, the prevalence of CKD is 0.38%, or approximately 713,783 people.⁴ Meanwhile, 11% of patients with stage 3 chronic kidney disease progressed to end-stage renal disease requiring hemodialysis due to untreated renal fibrosis.⁵ In addition, the prevalence of ongoing dialysis among individuals aged ≥ 15 years with a history of diagnosed chronic kidney disease in Indonesia was 19.3%.⁴

Hepatitis C can occur in chronic kidney patients undergoing hemodialysis, as evidenced by research conducted by Widhani in 2017, which found a prevalence of 38% of hepatitis C in patients on hemodialysis.⁶ Another study found that the prevalence of hepatitis C in patients on hemodialysis is still high, at 27.2%.⁷ Transmission of hepatitis C in patients undergoing hemodialysis is caused by a single factor, i.e., nosocomial transmission. This occurs because of failures to implement infection prevention protocols, such as inadequate surface disinfection, medical personnel not changing gloves after handling patients, drug preparation in contaminated areas, and poor hand hygiene practices.⁸

Hepatitis C transmission in hemodialysis units can be controlled with direct-acting antiviral (DAA) treatment. Several clinical

trials have shown that DAA regimens are more effective than previous treatments. DAAs are well tolerated, have low relapse rates, and require shorter treatment durations.⁹ Some DAAs also showed high cost-effectiveness.

Recommendations for hepatitis C treatment in patients with chronic kidney disease undergoing hemodialysis include grazoprevir/elbasvir, of which less than 1% is excreted through the kidneys.¹⁰ Based on the C-EDGE study, the SVR of 12 patients with hepatitis C undergoing hemodialysis using grazoprevir/elbasvir was 92%.¹¹ However, grazoprevir/elbasvir, when given to patients undergoing hemodialysis, is only effective for genotypes 1 and 4.¹⁰

The first publication on sofosbuvir-based therapy in patients undergoing hemodialysis was in 2017, specifically sofosbuvir/daclatasvir. According to research conducted by Ghanaat (2021), sofosbuvir/daclatasvir therapy administered to patients with hepatitis C undergoing hemodialysis showed an SVR of 97.2%.¹² Sofosbuvir/daclatasvir can be given to patients with chronic kidney disease undergoing hemodialysis with all genotypes, i.e., 1a, 1b, 2, 3, 4, 5, and 6.¹³

Sofosbuvir/daclatasvir treatment is more economical compared to grazoprevir/elbasvir. The cost of sofosbuvir/daclatasvir is 15 times lower than that of grazoprevir/elbasvir. Therefore, treatment with sofosbuvir/daclatasvir can significantly reduce the cost of treating hepatitis C in patients with chronic kidney disease undergoing hemodialysis. This approach will greatly contribute to the World Health Organization's (WHO) 2030 target to eliminate hepatitis by reducing its incidence by 90% and its mortality rate by 65%.¹⁴ Thus, in this study, we aimed to compare the efficacy and safety of sofosbuvir/daclatasvir with grazoprevir/elbasvir in patients with chronic hepatitis C undergoing hemodialysis.

METHODS

This was a randomized, single-blinded clinical trial to compare the efficacy and safety of sofosbuvir/daclatasvir with grazoprevir/elbasvir in patients with chronic hepatitis C undergoing hemodialysis. The researchers randomized the regimens using systematic random sampling. The researchers administered the regimens alternately to ensure a balanced distribution of patients across the two treatment groups.

Patients

A total of 120 chronic hepatitis C patients with CKD on hemodialysis were selected at Cipto Mangunkusumo National General Hospital and its network hospitals (Hasan Sadikin Hospital, Wahidin Sudirohusodo Hospital, Kariadi Hospital, and Moewardi Hospital). The inclusion criteria were patients aged ≥ 18 years, patients with chronic kidney disease undergoing hemodialysis, patients with reactive anti-HCV, and treatment-naïve patients. Patients underwent clinical and laboratory examinations, including HCV RNA, AST, ALT, total bilirubin, and liver stiffness.

The sample size was calculated based on the expected difference in SVR12 between the two treatment groups. Assuming a two-sided α of 0.05, 80% power, and a minimum clinically relevant difference of 10%, a total of 108 participants were required. To account for an estimated 10% dropout rate, the final target sample size was set at 120 participants (60 per group).

This study included two treatment groups. In the first group, patients received sofosbuvir/daclatasvir combination (400 mg/60 mg), while in the second group, patients received grazoprevir/elbasvir (100 mg/50 mg). Patients with fibrosis results $\geq F4$ were given sofosbuvir/daclatasvir for a treatment duration of 24 weeks. Patients with fibrosis $< F4$ were randomized to receive either sofosbuvir/daclatasvir or grazoprevir/elbasvir for 12 weeks. Patients with cirrhosis (F4) were not randomized because grazoprevir/elbasvir is contraindicated in advanced fibrosis and compensated/decompensated cirrhosis, as stated in the latest guideline.^{18,19,20} Therefore, all F4 patients received sofosbuvir/daclatasvir for clinical necessity. Patients with fibrosis $< F4$ were eligible for random allocation to either regimen.

Randomization was restricted to patients with fibrosis $< F4$. Eligible participants were randomized in a 1:1 ratio to receive sofosbuvir/daclatasvir or grazoprevir/elbasvir using a systematic random sampling sequence administered by the investigators. Allocation was single-blind, and participants were unaware of their treatment assignment. No allocation concealment procedure was applied.

After completing hepatitis C treatment, each patient was tested for treatment success (SVR) at week 12. Post-treatment safety for each regimen was monitored monthly after starting DAA treatment. The primary efficacy measure for both sofosbuvir/daclatasvir and grazoprevir/elbasvir was SVR12, determined by a quantitative polymerase chain reaction (PCR) test for HCV RNA; undetectable HCV RNA indicated success.

Statistical Analysis

Statistical analyses were conducted using SPSS version 24. Continuous data were reported as the median (range), and categorical data as proportions (%). Between-group comparisons were assessed using the Mann-Whitney test for continuous data and the chi-square test for categorical data.

Ethics and Integrity Statement

The Ethics Committee of the Faculty of Medicine, Universitas Indonesia, approved the study on September 19, 2022 (ethical clearance certificate No. KET-1002/UN2.F1/ETIK/PPM.00.02/2022), and informed consent was obtained from each participant prior to their involvement in the study.

RESULTS

The total sample included in this study consisted of 120 patients with hepatitis C undergoing hemodialysis (**Figure 1**). No dropouts, missing SVR12 values, or incomplete laboratory data were observed. Consequently, no imputation procedures were required. The absence of missing data strengthened the analysis's internal validity.

Of these, 60 patients received sofosbuvir/daclatasvir, and 60 patients received grazoprevir/elbasvir (**Table 1**). In the sofosbuvir/daclatasvir group, the median age was 51 years, and most

patients were male (53.3%). More than half of the patients were diagnosed with cirrhosis, with 73.3% having fibrosis stage F4. Most patients reported no adverse events (98.3%), and only 1.7% experienced nausea.

In the grazoprevir/elbasvir group, the median age was 52 years, and most patients were male (65%). All patients in this group received therapy for 12 weeks (100%). Most patients in this group had fibrosis stages F0-F1 (71.7%),

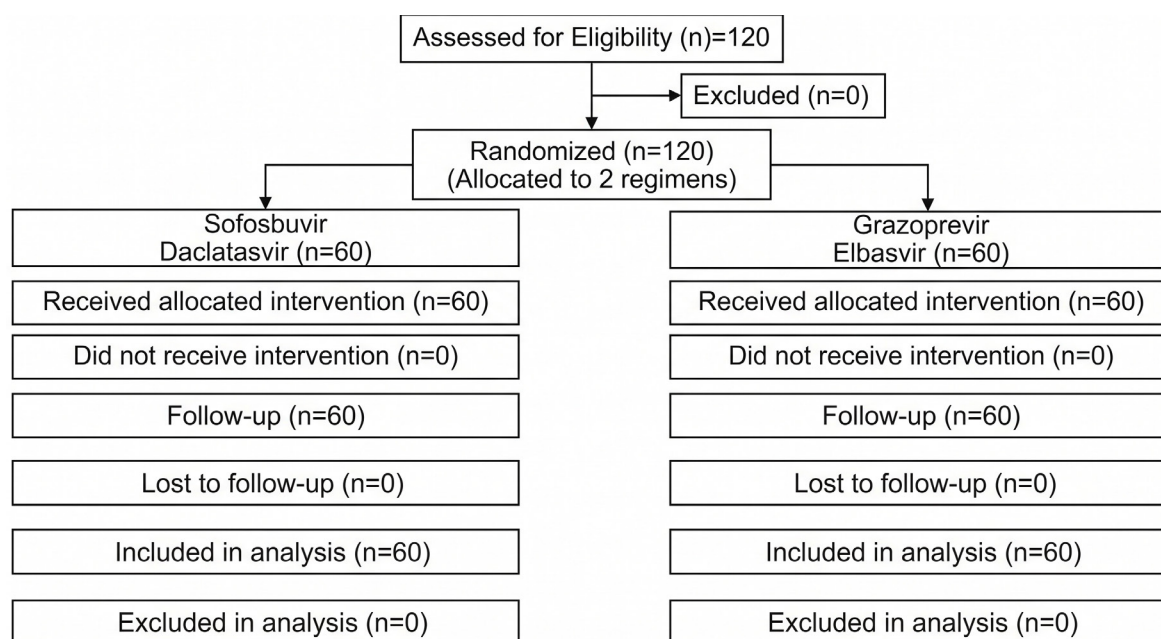


Figure 1. CONSORT flow diagram showing participant enrollment, randomization, allocation to sofosbuvir/daclatasvir or grazoprevir/elbasvir, follow-up, and inclusion in the final analysis.

Table 1. Baseline Characteristics and Clinical Condition of Study Participants

Variable	Sofosbuvir/Daclatasvir (n = 60)	Grazoprevir/Elbasvir (n = 60)	p-Value
Age, years, median (min-max)	51 (28-71)	52 (29-70)	0.297
Sex			0.265
Male	32 (53.3)	39 (65)	
Female	28 (46.7)	21 (35)	
Duration of Treatment			
24 weeks, n (%)	44 (73.33)	0 (0)	< 0.01
12 weeks, n (%)	16 (26.67)	60 (100)	
Fibrosis Stage			
F0-F1, n (%)	9 (15)	43 (71.7)	
F2-F3, n (%)	7 (11.7)	17 (28.3)	
F4, n (%)	44 (73.3)	0	
HCV RNA			
HCV RNA baseline, median (min-max)	4.95 x 10 ⁵ (10 ¹ - 11.8 x 10 ⁷)	7.71 x 10 ⁵ (12 x 10 ¹ - 14.4 x 10 ⁶)	
Laboratory			
AST	29.5 (8-238)	27.5 (5-214)	0.061
ALT	29 (4-261)	26.5 (4-189)	0.437
Total Bilirubin	0.76 (0.43-3.70)	0.66 (0.29-1.26)	0.052
Urea	92 (51.40-159.40)	96.3 (47.10-220.40)	0.009
Creatinine	7.8 (3-13.6)	10.2 (4.5-18.10)	0.066
eGFR	6.9 (3.4-89.0)	4.75 (2.8-34)	0.250
Adverse Event			
Nausea	1 (1.7)	0	
Drowsiness	0	1 (1.7)	
None	59 (98.3)	59 (98.3)	

and no patients were diagnosed with cirrhosis (0%). Most patients reported no adverse events (98.3%), with only 1.7% reporting drowsiness.

Median HCV RNA baseline in sofosbuvir/daclatasvir and grazoprevir/elbasvir was 4.95×10^5 (101 - 11.8×10^7) vs 7.71×10^5 (12×10^1 – 14.4×10^6); $p=0.004$. All patients in this study, in both the sofosbuvir/daclatasvir and grazoprevir/elbasvir groups, achieved SVR-12 of 100% (**Figure 2**).

In the sofosbuvir/daclatasvir and grazoprevir/elbasvir groups, post-treatment AST decreased with normal medical indicators, i.e., 16 (6-40) vs. 14 (5-29). The post-treatment median ALT was also reduced with normal medical indicators in the sofosbuvir/daclatasvir and grazoprevir/elbasvir groups, i.e., 10.5 (4-52) vs. 7.5 (4-48). Total bilirubin decreased in the sofosbuvir/daclatasvir and grazoprevir/elbasvir groups, with a median of 0.61 (0.26-1.28) vs. 0.62 (0.29-1.42). Urea also decreased post-treatment in the sofosbuvir/daclatasvir and grazoprevir/elbasvir groups, with a median of 80.7 (29-201.2) vs. 70.4 (13.7-175.60). Post-treatment creatinine also decreased in the sofosbuvir/daclatasvir and grazoprevir/elbasvir groups, with a median of 8.1 (0.8-15.6) vs. 9.25 (4.1-18.20). Also, post-treatment eGFR in the sofosbuvir/daclatasvir

and grazoprevir/elbasvir groups decreased, with a median of 5.25 (2.4-95.2) vs. 4.2 (2.3-25.3).

DISCUSSION

Hepatitis C virus infection can be transmitted in hemodialysis units. Nosocomial infection is one transmission factor. Additionally, shared hemodialysis machines increase the risk of cross-transmission. Based on previous research, the use of shared machines carries a risk of hepatitis C transmission, with an odds ratio (OR) of 1.3 (95% CI: 0.9–1.8) in anti-HCV patients with genotype 2a/2c.¹⁵ Duration of hemodialysis is also one of the factors contributing to hepatitis C transmission. Previous studies have linked hemodialysis duration to seroconversion from negative to positive anti-HCV. Another study found that a hemodialysis duration of more than 5 years was associated with the incidence of hepatitis C, with an odds ratio (OR) of 3.11 (95% CI: 1.57–13.71).¹⁶

Hepatitis C in patients on hemodialysis can be treated with direct-acting antiviral (DAA) treatment. DAA therapy shows better SVR rates, shorter treatment durations, and a relatively low toxicity profile.¹⁷

This study used two DAA regimens: sofosbuvir/daclatasvir and grazoprevir/elbasvir.



Figure 2. SVR-12 Rates by Direct-Acting Antiviral

Based on the European Association for the Study of the Liver (EASL), American Association for the Study of Liver Disease (AASLD), and Asian Pacific Association for the Study of the Liver (APASL), the sofosbuvir-based regimen is approved for use in patients with chronic kidney disease with an eGFR ≤ 30 mL/min or in patients undergoing hemodialysis.^{18,19,20}

This study shows that among patients with hepatitis C undergoing hemodialysis and treated with sofosbuvir/daclatasvir, 73% had cirrhosis. Treatment efficacy with DAAs was generally lower with longer treatment durations. However, this study demonstrates that using sofosbuvir/daclatasvir resulted in a 100% SVR12 outcome. These results align with research by Bhat (2023), which found 100% efficacy of sofosbuvir/daclatasvir therapy in patients with hepatitis C undergoing hemodialysis.²¹ According to a systematic review, therapy with sofosbuvir/daclatasvir also achieves an SVR-12 rate of 100% in patients with hepatitis C undergoing hemodialysis.²² Another study conducted by Cheema (2019) also showed that the success rate of daily sofosbuvir/daclatasvir therapy in patients with kidney disease undergoing hemodialysis was 100%.²³ The pharmacodynamics of the sofosbuvir/daclatasvir regimen showed side effects, such as headache, diarrhea, and nausea.²⁴ In the results of this study, adverse events associated with sofosbuvir/daclatasvir therapy included nausea in 1.7% of patients. Based on a systematic review of the side effects of sofosbuvir in patients on hemodialysis, nausea and vomiting were reported in 14% of cases (95% CI: 4–27%).²⁵ This shows that sofosbuvir given to patients with hepatitis C undergoing hemodialysis is safe and effective.

This study also found that the SVR-12 result for therapy with grazoprevir/elbasvir in patients with hepatitis C undergoing hemodialysis was 100%. Another study by Ji (2021) also found 100% efficacy with grazoprevir/elbasvir in patients with hepatitis C undergoing hemodialysis.²⁶ The efficacy of grazoprevir/elbasvir in patients on hemodialysis was SVR 12 of 98.5%.²⁷ Another study also found an SVR-12 of 96.9% in patients with hepatitis C undergoing hemodialysis treated with grazoprevir/elbasvir.²⁸ Another

success rate is supported by other studies, which found that patients with hepatitis C undergoing hemodialysis who received grazoprevir/elbasvir therapy achieved an SVR-12 of 96.7%.²⁹ Based on the data above, the efficacy study of grazoprevir/elbasvir in patients with hepatitis C undergoing hemodialysis showed better SVR-12 results compared to previous studies. The pharmacodynamics of grazoprevir/elbasvir indicate that side effects may occur, such as fatigue, headache, and nausea.²⁶ This study found that an adverse event, specifically drowsiness, occurred in 1.7% of patients.

In this study, the success rate (SVR-12) for both sofosbuvir/daclatasvir and grazoprevir/elbasvir was 100%. This study did not assess subjects' genotypes. However, the subjects were treated with different regimens based on their fibrosis stage. Patients with fibrosis stage F4 were not given grazoprevir/elbasvir, while patients with stages other than F4 could be randomized to either regimen. This approach is supported by the European Association for the Study of the Liver (EASL) and the American Academy of Family Physicians, as grazoprevir/elbasvir is contraindicated in patients with cirrhosis.^{19,30}

This study is the first to evaluate the efficacy and safety of sofosbuvir/daclatasvir with grazoprevir/elbasvir in patients with chronic hepatitis C undergoing hemodialysis across various hospitals in Indonesia. Second, sofosbuvir/daclatasvir and grazoprevir/elbasvir therapy has been shown to be effective and safe for patients with hepatitis C undergoing hemodialysis, with a significant sample size in the Indonesian population. Thirdly, sofosbuvir/daclatasvir can be used for all genotypes 1a, 1b, 2, 3, 4, 5, and 6, and can be administered to patients with cirrhosis. Fourth, sofosbuvir/daclatasvir costs 15 times less than grazoprevir/elbasvir. Last but not least, sofosbuvir-based regimens have also been safely used and are recommended by EASL, APASL, and AASLD for patients with hepatitis C undergoing hemodialysis.

Nonetheless, several limitations remain. Genotype testing was not performed, restricting interpretation of regimen-specific efficacy, particularly for grazoprevir/elbasvir. Baseline fibrosis severity also differed between groups

because of clinical eligibility criteria, which may have introduced residual confounding. The single-blind design and absence of allocation concealment raise the potential for bias. Finally, laboratory follow-up was limited to 12 weeks post-treatment, preventing assessment of longer-term safety outcomes.

CONCLUSION

Sofosbuvir/daclatasvir and grazoprevir/elbasvir are effective and safe for patients with hepatitis C undergoing hemodialysis. Sofosbuvir/daclatasvir is effective across all fibrosis stages and has lower regimen costs for patients in developing countries. Meanwhile, the grazoprevir/elbasvir regimen is effective for fibrosis stages F0-F1 and F2-F3 without cirrhosis but costs more.

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CONFLICT OF INTERESTS

Each author declares no conflicts of interest related to this work.

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