ORIGINAL RESEARCH PAPER

Gastroenterology

SAFETY AND EFFICACY OF DIRECT ACTING ANTIVIRALS FOR CHRONIC HEPATITIS C IN PATIENTS WITH CHRONIC KIDNEY DISEASE ON MAINTENANCE HEMODIALYSIS

KEY WORDS:

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ABSTRACT

BACKGROUND AND AIMS: Hepatitis C virus (HCV) infection is common among hemodialysis (HD) patients and is associated with increased morbidity and mortality. Aim of the study is to assess the safety and efficacy of pangenotypic DAA regimens in patients with chronic disease on maintenance hemodialysis. **MATERIALS AND METHODS:** In this prospective observational study, hemodialysis patients with chronic hepatitis C infection were identified and treatment initiated with appropriate pangenotypic regimen. Totally 74 patients diagnosed with chronic hepatitis C and treated with DAAs for 12 weeks. The sustained virologic response (SVR) rate obtained 12 weeks post-treatment (SVR12) was evaluated. Laboratory indices and adverse reactions during the treatment process were also assessed. **RESULTS:** All the patients enrolled completed 12 weeks of treatment. 12 out of 74(16.2%) patients had compensated liver disease. SVR was achieved in 12 out of 12 patients (100%) receiving sofosbuvir/velpatasvir, and 60 of 62 patients (96.7%) receiving sofosbuvir/daclatasvir. No serious or significant adverse reactions were reported. **CONCLUSION:** Pangenotypic regimens containing sofosbuvir are safe and well tolerated in patients with chronic kidney disease on maintenance hemodialysis. Sofosbuvir/daclatasvir based regimens at full dose can be used as an alternative pan genotypic regimen in patients with chronic kidney disease on hemodialysis.

1. INTRODUCTION

Prevalence of HCV infection is common among patients on hemodialysis. The frequency of anti-HCV positivity in HD patients varied from 1.6% to 68% in the world (1). The risk of all-causes and liver-related mortality is higher in HD patients with HCV infection (2). Previously, treatment of individuals infected with HCV was limited to interferon- and ribavirin (RBV)-containing regimens, with low cure rates and serious and unpleasant side effects (3). DAAs have become the first-line treatment option for chronic HCV, due to high efficiency, low resistance and high safety, as recommended by international guidelines(4)(5). Indian data regarding assessment of efficacy and safety in hemodialysis patients are scarce. Therefore, the present study aimed to assess the effectiveness and adverse event of DAAs in maintenance hemodialysis patients complicated with chronic hepatitis C in our center.

2. PATIENTS AND METHODS

All patients who visited the outpatient department of medical gastroenterology for "chronic hepatitis C" from January 2021 to December 2021 for antiviral treatment were screened, and those with hemodialysis were enrolled. Chronic hepatitis C was confirmed by ELISA method and RNA PCR was done for viral load quantification.

INCLUSION CRITERIA:

1) Chronic kidney disease (CKD) patients on hemodialysis and are anti HCV positive and who completed 12 weeks of DAA therapy.
2) Treatment naïve patients

EXCLUSION CRITERIA:

1) Patients who did not complete DAA therapy
2) Hepatitis B positive
3) Post renal transplant
4) History of treatment of HCV
5) Hepatocellular carcinoma

2.2. Treatment plan and follow-up

Before treatment, all the patients included had undergone blood biochemistry, blood routine, coagulation function examination. Blood samples from all patients were collected before hemodialysis on the same day. Ultrasound was done to diagnose patients with cirrhosis of liver. [6]

2.3. Study outcomes

Sustained virologic response, defined as undetectable HCV RNA, was assessed at 12 weeks posttreatment. The primary efficacy endpoint was SVR12. Safety was primarily assessed by the proportion of patients who discontinued the treatment because of adverse drug reactions; in addition, patient safety over the course of treatment (drug-related or suspected adverse reactions reported by patients or their families) was assessed.

2.4. Data collection

Demography data, including gender, age, HCV RNA, HCV genotype, and comorbidities, were collected from medical records or interviews.

2.5. Statistical methods

The SPSS 25.0 software (SPSS, USA) was used for statistical analysis. Baseline and endpoint data were summarized by descriptive statistics. $P<.05$ was considered Statistically significant.

3. RESULTS

3.1 Baseline characteristics

There were 74 hemodialysis patients complicated with hepatitis C, including 22 females and 52 males with an average viral load of 5x107 IU/ml. All patients are treatment naïve. 30 cases were concurrently complicated with diabetes,

hypertension and coronary artery disease. 12 patients had compensated liver disease. (Table 1)

Basic features of enrolled patients	n = 74
Age in years	43.6yrs (15 to 74)
Sex	Male- 52 female - 22
Average viral load	5x107 u/ml
cirrhosis	12/74(16.2%)
diabetes	16/74(21%)
hypertension	30/74(40%)
Coronary artery disease	10/74(13%)

3.2. Treatment plans

PATIENT CHARACTERISTICS	REGIMEN	DURATION
CKD+CIRRHOSIS	SOFOSBUVIR 400MG + VELPATASVIR 100MG	12 WEEKS
CKD	SOFOSBUVIR 400MG + DACLATASVIR 60MG	12 WEEKS

3.3 Treatment effects and safety

No serious adverse reactions were noted during the treatment. All the patients were compliant with drug intake. Viral load was undetectable in 72 out of 74 patients 12 weeks post treatment. 2 patients who received sofosbuvir/ daclatasvir had detectable viral load 12 weeks post treatment.

PATIENT CHARACTERISTICS	REGIMEN	SVR 12
CKD+CIRRHOSIS	SOFOSBUVIR 400MG + VELPATASVIR 100MG	12/12 (100%)
CKD	SOFOSBUVIR 400MG + DACLATASVIR 60MG	60/62(96.7%)

DISCUSSION

Not many studies evaluated the efficacy of sofobuvir based regimens in patients with chronic liver disease. Regimens currently suggested include elbasvir/grazoprevir and glecaprevir/pibrentasvir. Glecaprevir/pibrentasvir alone is pangenotypic but it is not available in India.

This study aimed safety and efficacy of pangenotypic DAA regimens in patients with chronic kidney disease on maintenance hemodialysis. Liver disease-related mortality, cardiovascular mortality and infection-related mortality are all significantly increased in hemodialysis patients complicated with HCV infection (7). These patients tend to progress faster to cirrhosis and develop hepatocellular carcinoma if not treated (8). Sofosbuvir has predominant renal excretion; toxicity with sofosbuvir has not been documented even though very high serum levels of the metabolite have been documented in patients with ESRD (9).

In our study, we used two fixed dose regimens, sofosbuvir400/velpatasvir 100mg, sofosbuvir400/ daclatasvir 60mg, for the therapy, which attained 97.29% SVR at week 12 post treatment (100% with sofosbuvir/velpatasvir, 96% with sofosbuvir/ daclatasvir). Our results are consistent with recent study by taneja s et al., in which SVR was attained in 96% of patients on treatment with sofosbuvir and velpatasvir (10). In contrast to other studies, genotyping was not done and sofosbuvir/daclastasvir was evaluated as a pangenotypic regimen in our study. The number of patients with cirrhosis was less in our study [12 (16%) vs 17 (29%)] as compared to the study by Borgia et al, and all patients belonged to CHILD CLASS A, which might be the reason for such an excellent response in our study without major side effects(11). Similarly, study by gaur et al, in treatment naïve patients assessed the efficacy of sofosbuvir/velpatasvir fixed dose regimens, with an efficacy of 96.8% vs. 100 % in our study (12). Study by poustchi H et al., showed 100% SVR with sofosbuvir and daclatasvir, but our patients who received sofosbuvir/daclatasvir SVR was achieved in 96.7% of patients (13).

Plasma levels of sofosbuvir was not evaluated, nevertheless absence of adverse effects suggest relative safety of the drug. Since all the patients were on hemodialysis, adverse effects might be less. Routine use in chronic kidney patients not on hemodialysis needs further studies to document safety.

CONCLUSION

The results of our study show that, sofosbuvir/daclatasvir fixed dose regimen is as effective as sofosbuvir/velpatasvir regimen, without significant adverse effects and routine genotype evaluation is not required. Sofosbuvir based regimens can be prescribed at full dose with minimal monitoring as in non-CKD patients.

LIMITATIONS OF OUR STUDY

1) Number of patients with cirrhosis is less
2) All patients are treatment naïve
3) Patients with decompensated chronic liver disease need to be studied.
4) Patients with chronic kidney disease not on hemodialysis were not considered

REFERENCES

1) Fabrizi F, Dixit V, Messa P. Hepatitis C virus and mortality among patients on dialysis: A systematic review and meta-analysis. Clin Res Hepatol Gastroenterol. 2019; 43:244-254.
2) Pawlotsky JM, Negro F, Aghemo A, Berenguer M, Dalgard O, Dusheiko G, Marra F, Puoti M, Wedemeyer H. EASL recommendations on treatment of hepatitis C 2018. J Hepatol. 2018;69:461-511.
3) Collier S, Davenport A. Reducing the risk of infection in end-stage kidney failure patients treated by dialysis. Nephrol Dial Transplant 2014;29:2158–61.
4) Khaliq S, Raza SM. Current status of direct acting antiviral agents against hepatitis C virus infection in Pakistan. Medicina (Kaunas) 2018;54:80.
5) Frisk P, Aggefors K, Cars T, et al. Introduction of the second-generation direct-acting antivirals (DAAs) in chronic hepatitis C: a register-based study in Sweden. Eur J Clin Pharmacol 2018;74:971–8.
6) Cardoso AC, Carvalho-Filho RJ, Stern C, et al. Direct comparison of diagnostic performance of transient elastography in patients with chronic hepatitis B and chronic hepatitis C. Liver Int 2012;32:612–21.
7) Fabrizi F, Dixit V, Messa P. Impact of hepatitis C on survival in dialysis patients: a link with cardiovascular mortality. J Viral Hepat 2012;19:601–7
8) Lee CH, Hsieh SY, Chang CC, Wang IK, Huang WH, Weng CH, et al. Hepatocellular carcinoma in hemodialysis patients. Oncotarget. 2017;8(42):73154-61.
9) Isnard Bagnis C, Cacoub P. Hepatitis C Therapy in Renal Patients: Who, How, When? Infect Dis Ther. 2016;5(3):313-27.
10) Taneja, S, Duseja, A, Mehta, M, et al. Sofosbuvir and Velpatasvir combination is safe and effective in treating chronic hepatitis C in end-stage renal disease on maintenance haemodialysis. Liver Int. 2021; 41: 705– 709.
11) Borgia SM, Dearden J, Yoshida EM, Shafran SD, Brown A, Ben-Ari Z, et al. Sofosbuvir/velpatasvir for 12 weeks in hepatitis C virus-infected patients with end-stage renal disease undergoing dialysis. J Hepatol. 2019;71(4):660-5.
12) Gaur N, Malhotra V, Agrawal D, Singh SK, Beniwal P, Sharma S, et al. Sofosbuvir-Velpatasvir Fixed Drug Combination for the Treatment of Chronic Hepatitis C Infection in Patients With End-Stage Renal Disease and Kidney Transplantation. J Clin Exp Hepatol. 2020;10(3):189-93.
13) Poustchi, H., Majd Jabbari, S., Merat, S.,et.al., (2020) The combination of sofosbuvir and daclatasvir is effective and safe in treating patients with hepatitis C and severe renal impairment. Journal of Gastroenterology and Hepatology, 35: 1590– 1594