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Original Research Article

Outcome of sofosbuvir based regimen in chronic hepatitis C patients with chronic kidney diseases on maintenance hemodialysis from western India

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Abstract

Introduction: The introduction of direct-acting antiviral (DAA)-based therapies for hepatitis C virus (HCV) has revolutionized the approach to HCV treatment. The data of sofosubvir based regimen in HCV infected Chronic Kidney Diseases (CKD) Patients on maintenance hemodialys (MHD) is not widely available. Our study was aimed to evaluate the effect of sofosbuvir–Ledipasvircombinationregimen in HCV positive CKD patient on MHD.

Materials and Methods: Patients aged more than 12 years with HCV RNA positive and on MHD were included. Patients having liver cirrhosis and already started DAAs were excluded. Before starting treatment genotype, viral load routine clinical and laboratory data (CBC, SGPT, S.Albumin, S.Fetoprotein) were collected at baseline and also at 4, 12, and 24weeks during the treatment. All patients irrespective of genotypes were started sofosbuvir 400mg plus Ledipasvir 90 mg combination alternate day for 12 weeks. HCV RNA viral load was assessed at the end of 4, 12 and 24wks.We evaluated early virological response (EVR) at end of 4th weeks, end of treatment response (ETR) at the end of 12 weeks and sustained virological response (SVR) at the end of 24 weeks after initiation of therapy.

Results: We had enrolled 210 HCV RNA patients with male (n=166) predominance with mean age of 31.6±10 years. Genotype 1 in 179 (85.2%) and genotype 3 in 31(14.8%) were found. 208 patients (99.03%) had achieved complete response at 12 wks (SVR_{12}). 2 patients (1b,3) did not respond even at 24 wks. None of patient discontinued therapy because of side effects. No significant change in hemoglobin, platelet count and bilirubin.

Conclusions: Sofosbuvir-Ledipasvir therapy on alternate day for 12 weeks was found effective therapy for HCV-infected CKD patients on MHD.

Keywords: Sofosbuvir, Ledipasvir, HCV treatment, Haemodialysis, Western India.

Introduction

Hepatitis C Virus (HCV) infection is very common infection in patients with chronic kidney diseases (CKD) on maintenance hemodialysis (MHD). It is an important cause of liver disease. HCV infection is major public health problem and associated with increased mortality and morbidity among patients on MHD. Hepatitis C virus (HCV) infects 3% of the world population, and its prevalence in our country is about 4.3% to 45%.[1-3] HCV is an enveloped, positive single-stranded RNA virus belongs to genus Hepcivirus and family Flaviviridae. HCV genome comprise highly conserved and highly variable regions Based on the sequence divergence, till date, HCV strains are divided into seven main genotypes and multiple subtypes, 67 confirmed and 20 provisional subtypes.[3] HCV genome has relatively well-conserved regions used as basis for classification. The highly variable region is envelope 2 (E2).[4] HCV genome contains structural proteins like core[C], envelope [E1 and E2] and the non-structural proteins like NS1, NS2, NS3, NS4A, NS4B, NS5A, and NS5B.[4] The high replicative activity and lack of proof-reading capability of the RNA-dependent RNA polymerase makes HCV virus high genetic heterogeneous.[5,6]The conventional antiviral therapy against HCV is either mono therapy with interferon (IFN) that may be pegylated or in combination with ribavirin and associated with poor tolerability, low efficacy and unacceptably high rates of acute kidney injury, acute rejection and graft failure before the availability of direct-acting antiviral agents (DAA).[7]The administration of DAA therapy represents a new and effective option for CKD patients population on maintenance hemodialysis and acquiring HCV negative status before transplant as well as option of treating HCV positivity after transplantation on individual case basis has revolutionized post-transplant management and outcome of HCV positive recipients. DAA effect on NS5B, RNA-dependent RNA polymerase, the NS5A phosphor proteinand NS3 protease, were created miracle with minimum side effect, short therapy and sustained virological response rates of 60-100%.[8-10]Sofosbuvir (SOF) is a promising therapy for chronic HCV infection, It competitively blocks the NS5B polymerase, thus inhibiting the HCV-RNA synthesis by RNA chain termination.[11,12] The catalytic site of the enzyme is also highly conserved across all the HCV genotypes, accounting for pan-genotypic efficacy of sofosbuvir.[13] It has got FDA approval on 2013,

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http://doi.org/10.18231/j.ijmmtd.2019.029

under the breakthrough therapy designation. This drug is effective against all HCV genotypes, has a better safety profile, and low risk of development of resistance; however, careful clinical use and monitoring is still essential, to gather more data on this drug. We evaluated our experience on Sofosbuvir based regimens in HCV infected CKD patients on MHD and who were awaiting renal transplant. Therefore, our study was aimed to establish outcome of Sofosbuvir based regimen in treatment of hepatitis C patients with chronic kidney disease on maintenance hemodialysis from western India.

Materials and Methods

This was a prospective single center study carried out from Sept'17 to June'19 after IEC approval. We had enrolled 210 patients with CKD who were HCV RNA positive and were on maintenance hemodialysis of both genders, aged more than 12 years were included in the study. Patients already under treatment for HCV infection and liver cirrhosis were excluded from the study. The study population was explained about nature of the study and informed consent was taken before the study. For patients > 12 and < 18 years of age, informed consent was obtained from parents. Patients with reactive anti-HCV antibodies were further investigated for their qualitative HCV RNA, HCV viral load, and HCV genotype before starting the treatment. Before starting treatment Routine clinical and laboratory data (CBC, SGPT, bilirubin, S. Albumin, S. Fetoprotein) were evaluatedat baselineand 4, 12, and 24weeks during treatment. All patients irrespective of genotypes were started sofosbuvir 400 mg plus Ledipasvir 90mg combination alternate day for 12 weeks. HCVRNA viralload was assessed at day 0, 4wks, at the end of therapy at 12 wksandat the 24 wks. We evaluated early virological response (EVR)that is defined as undetectable HCV RNA titer at 4weeks after initiation of therapy, end of treatment response (ETR) that is defined as undetectable HCV RNA titer at 12 weeks after initiation of therapy, and sustained virologicalresponse (SVR) is defined asundetectable HCV RNA titerat the end of 24weeks after initiation of therapy. Patients were asked to report adverse effects to investigator. Descriptive statistics was used to present the data.

Results

We screened 230 patients with positive anti HCV antibody for HCV RNA titre and out of 230, 210 patients were positive for HCV RNA titre. Thus, 210 patients with positive HCV RNA were included in the present study.

Table 1: Demographic data and laboratory profile of the HCV RNA patients.

Age	**31.6 ± 10years**
Gender (Male: Female)	166:44
HCV RNA titre positive	210
Dialysis Duration (month)	17± 9 month
Hemoglobin (g/dl)	9.9±2.0
Platelet count	1.56± 1.0
Alanine aminotransferase (IU/dl)	40.8±30.4 (7-180)
Quantitative RNA copies (median and interquatile range)	10^5 (10^2 -$10^{8)}$
Alpha-fetoprotein (mg/dl)	3.01± 0.6 (2.3-6.3)

Genotype 1 was found in 179 (85.2%) and genotype 3 in 31(14.8%) patient. (Table 2)

Table 2: Genotype distribution of HCV among patients on MHD

Genotypes	**No (%)**
1a	128(60.95%)
1b	44(20.95%)
1ab	1(0.47%)
1	6(2.85%)
3a	22(10.47%)
3b	3(1.42%)
3	6(2.85%)

At the end of 4th week of therapy, EVR were achieved in 187(89%) patients At the end of 12 weeks ETR had achieved in 208pts (99%). Were develop. There was no difference in response rates regarding to genotype. Two patients who did notresponsebelonged to genotype 1b and genotype 3.SVR was developed in 208pts (99%). Virological breakthroughs were not detected in any patientduring and after therapy.

Table 3: Virological response of Sofosbuvir based therapy in HCV RNA positive patients

Genotype	**Prevalence of genotypes**	**4 week EVR**	**12 week ETR**	**24 Week SVR**
1a	128	120	128	128
1b	44	35	43	43
1ab	1	1	1	1
1	6	5	6	6
3a	22	20	22	22
3b	3	2	3	3
3	6	4	5	5
Total	210	187(89%)	208(99%)	208(99%)

None of patient discontinued therapy because of side effects. No significant change in hemoglobin, platelet count and bilirubin was found.

Discussion

In this study, we evaluated Sofosbuvir based therapy in HCV infected CKD patients on MHD which is probably the first largest single center study in Western India in this type of population. The efficacy and safety of DAA drugs in management of HCV-infected CKD patients has created revolution in renal medicine Li T et al. had done meta-analysis and showed SVR-12 of 93.2% patients with stage 4 and stage 5 with DAA therapy in ESRD patients, which was matching with our finding of SVR-12 in 99.% patients of

HCV infected CKD patients.[14] In another multicenter study performed by Ueda et al, in chronic HCV infected 54 post-liver transplant patients with genotype 1b treated with SOF/LDV without ribavirin for 12 weeks.[15] EVR was reported as 52% at 4 weeks, and ETR at 12th weeks and SVR ratio were 98% which was matching with our finding of ETR and SVR in 99% patients of HCV infected CKD patients. Desnoyer et al, showed that SOF and its active metabolites did not accumulate in patients on hemodialysis and suggested use of 400 mg/d SOF with close monitoring.[16] We therefore used full dose sofosbuvir with ledipasvir 90 mg combination alternate day for 12 weeks for MHD patients without liver cirrhosis.

Our finding was also supported by the study of Agarwal SK et al who showed SOF-based therapy in HCV patients on hemodialysis showing very good efficacy and safety of the drug.[17]All patients were treated by SOF regimen for 12 weeks. By the 14thday,viral load undetectable in Sixty (96.8%) patients whereas all patients (100%) had achieved EVR by week 4, and there was no virologic breakthroughs on therapy.[17] In a study by Fernández et al, which was performed in 103 renal transplant patients treated with DAAs for chronic HCV, EVR achieved in 59% patients at 4 weeks after the initiation of treatment and ETR were developed in 98% of patients at the end of treatment, and SVR12 ratio achieved was 98%.[18] The majority of these patients were genotype 1 (83%), and 57% of them were administered SOF/ledipasvir with or without ribavirin. Patients treated with or without ribavirin, treated over 12 or 24 weeks, or between cirrhotic and non-cirrhotic patientswas no difference in treatment response which was matching with our study finding like patients with genotype 1 were 85% and genotype 3 15% HCV infected CKD patients treated by SOF regimenachievedVR-12 in 99% of HCV infected CKD patients on MHD. Singh et al., USA had studied effect of SOF, ledipasvir, simeprevirin CKD patients and showed thatSVR-12 achieved was about 87.5%, which was lesser than what we achived.[19] Nazarioet al., a study from USA had explained an effect of sofosbuvirmono therapy in 100 patients and established all were genotype 1 and had achieved SVR-12 of 97.2%agreed with our study.[20] Beinhardt had done analysison SOF, daclatasvir and ribavirin in patients with genotype 1(60), genotype3 (20), genotype 4(20) and showed SVR-12 of 95.5%.[21] Saxena et al. analyzed effect of SOF, simeprevir, ribavirin, drugs on genotype 1(78), Genotype 2(17) and Genotype 3(6) and achieved SVR-12of 88.2%.[22]

Conclusion

Sofosbuvir- Ledipasvir therapy on alternate day for 12 weeks was found effective therapy for HCV-infected CKD patients on MHD. It caused early virologicalresponse in 89% patients (at 4wks) and sustained virological response in 99% patients (at 24wks).

Acknowledgements

The authors are first thankful to all volunteer participants enrolled in this PhD study. Authors are thankful to the Director of our Institute, Dr. Vineet V. Mishra, for giving permission to conduct this study and also thankful to the members of Institutional Ethics Committee to grant the permission for conducting this PhD work. The authors are giving special thanks to Ms. Varsha B. Trivedi, Dr. Paulin Gandhi, Dr.Manish Barvaliya for immense help and also to lab technicians, hemodialysis technicians, nursing staff, and statistician for their help in study.

Conflict of Interest

None

Institutional clinical study No.

PhD study: IKDRCITS- LAB-10-02-2017

Primary researcher of PhD work

Dr. Minaxi H. Patel

Guide of PhD work

Dr. Pranay K. Shah

Ethical approval and consent to participate for PhD study

The study was approved by our institutional review board and study number was IKDRCITS- LAB-10-02-2017. Consent was obtained from all participants.

Consent for publication

Taken

Consent of patients

Obtained

Reference

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How to cite this article: Patel MH, Shah PK, Vanikar AV, Patel HV, Patel RD. Outcome of sofosbuvir based regimen in chronic hepatitis C patients with chronic kidney diseases on maintenance hemodialysis from western India. *Int J Med Microbiol Trop Dis* 2019;5(1):134-7.