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Original Article

Effectiveness of Combination Therapy of Sofosbuvir and Daclatasvir in Hepatitis C Positive Hemodialysis Patients Presenting to a Tertiary Care Hospital

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ABSTRACT

Objective: To determine the frequency of sustained virological response (SVR) after treatment with Sofosbuvir and daclatasvir among hepatitis C positive hemodialysis patients presenting to a tertiary care hospital.

Study Design: Descriptive case series.

Place and Duration of Study: Department of Nephrology, Sharif Medical City, Lahore Pakistan, from Mar to Dec 2019.

Methodology: Total 62 hepatitis C positive hemodialysis patients undergoing regular hemodialysis in the Heamodialysis unit of Sharif Medical City, Lahore and fulfilling the selection criteria were enrolled in the study after an informed consent. Information regarding their demographic data was noted in the proforma. All the patients were advised 400 mg of sofosbuvir on alternate day along with 60mg daclatasvir once daily for 12 weeks. At the end of 12 weeks of therapy, all patients were undergone qualitative PCR and effectiveness of the treatment was noted on the basis of qualitative PCR. In order to see SVR 12 PCR was repeated after 12 weeks and SVR labeled as operational definition.

Results: Total 62 patients were enrolled in the study. Their mean age was 36.52±14.03 years with range from 15-60 years. The minimum duration of dialysis was 3 months and maximum was 10 months. Body mass index ranged from 25-32 kg/m^2 with mean 28.37±2.29 kg/m^2. There were 53.2% male patients and 46.8% were female patients. SVR-12 was achieved in 82.3% patients while 17.7% patients failed to respond No association was found between SVR-12 and age, sex, BMI or duration of dialysis. No significant side effects were noted

Conclusion: Treatment with Sofosbuvir and daclatasvir among hepatitis C positive hemodialysis patients, resulted in SVR -12 in 51 out of 62(82.3%) patients while SVR-12 was not achieved in 11(17.7%) patients. Effect modifiers like age, gender, duration of dialysis and BMI did not show significant association with SVR.

Keywords: HCV, Hemodialysis, Sustained virological response, Sofosbuvir.

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INTRODUCTION

Hepatitis C and chronic kidney disease (CKD) are major global public health problems. Hepatitis C has affected more than 185 million people worldwide, of which 50-85% developed chronic infection resulting in development of cirrhosis and increased risk of hepatocellular carcinoma over long term.[1] The prevalence of CKD based on health screening camps and community in Pakistan has been found to be around 12.5-25% while the prevalence of hepatitis C positive among these patients is found to be 27.2%. Furthermore, fluid management of a patient with decompensated liver disease is difficult. Thus an effective treatment regime is the corner stone in improving the survival rate in these patients.[2] Various studies are available regarding the effectiveness of interferon, ribavarin and sofosbuvir in treatment of patients with hepatitis C but not much local literature is available regarding effectiveness of daclatasvir with alternate day regime of sofosbuvir in these patients. Assessing the natural history of hepatitis C among patients on maintenance hemodialysis is more difficult because of additional characteristics in this group of population.[3] Nephrologists have been reluctant to perform liver biopsy due to concern about abnormalities in platelet function in uremia. Aminotransferase activity is lower in patients with chronic renal failure than in normal population, and this may hamper recognition of HCV-related liver disease.[4] Although third-generation anti-HCV testing is specific and sensitive in patients with end-stage renal disease, earlier versions of anti-HCV testing have been less reliable in ESRD patients because of the blunted humoral immune response that is associated with renal disease: a small proportion of ESRD patients have HCV viremia, but lack detectable anti-HCV.[5]

Mortality is an identifiable complication of liver disease and a reliable end-point in the natural history of HCV-related liver disease.[6] Recent evidence indicates

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that HCV plays a detrimental effect on survival in the dialysis population, but it remains unknown whether the high mortality risk due to HCV infection is only attributable to an increase in liver disease-related deaths.[7] Chronic HCV infection is usually slowly progressive and may not result in clinically apparent liver disease in many patients if the infection is acquired later in life. Approximately 20-30% of chronically infected individuals develop cirrhosis over a 20-30 year time period.[8] Chronic HCV is the most common cause of chronic liver disease and the most frequent indication for liver transplantation in the United States. Early casecontrol studies of patients with newly acquired, symptomatic non-A, non-B hepa-titis found a signi-ficant association between disease acquisition and a history six months prior to illness of blood transfusions, IV drug use, health care employ-ment with frequent exposure to blood, personal contact with others who had hepatitis, multiple sexual partners or low socioeconomic status.[9] Studies have consistently shown that HCV infection is associated with an increased mortality in patients with ESRD.[7] In a meta-analysis by Fabrizi *et al*. the relative risk of mortality was 1.35 (95% confidence interval, 1.25-1.47) among HCV-infected patients with ESRD.[10]

METHODOLOGY

This descriptive case series study was conducted in Nephrology Department, Sharif Medical City Lahore Pakistan, form Mar to Dec 2019.

Inclusion Criteria: Hepatitis C PCR positive hemo-dialysis patients aged 15 to 60 years and both gender presenting in the nephrology department of Sharif Medical City, Lahore were enrolled into this study.

Exclusion Criteria: Previously treated patients and those not willing to participate in the study were not included in this study.

Sample size of 62 cases is calculated with 95% confidence level, 10% margin of error and taking expected percentage of effectiveness of treatment as 80%. Non-probability consecutive sampling technique was used. Total 62 hepatitis C positive hemodialysis patients undergoing regular hemodialysis session in the heamodialysis unit of Sharif medical city, Lahore and fulfilling the selection criteria were enrolled in the study after an informed consent. Information regarding their demographic data was noted in the proforma. All the patients were advised 400mg of sofosbuvir on alternate day along with 60 mg daclatasvir once daily for 12 weeks. At the end of 12 weeks of therapy, all patients were undergone qualitative PCR and effectiveness of the treatment were noted on the basis of qualitative PCR. In order to see SVR 12 PCR was repeated after 12 weeks and SVR12 labeled as operational definition. Data was entered and analyzed using statistical package for social sciences version 17.0. Numerical variable i.e. age was summarized as mean and standard deviation. Qualitative variables like sex and attainment of SVR 12 were presented in the form of frequency and percentages. Data was stratified for age, gender, BMI, duration of dialysis and chi square test was applied to compare the response between different groups. A *p*-value <0.05 was considered as statistically significant.

RESULTS

From 62 cases, it was observed that the minimum age was 15 years and maximum age was 60 years with mean and standard deviation of the age was 36.52± 14.03 years. The minimum Duration of Dialysis was 3 months and maximum was 10 months. The minimum body mass index was found as 25kg/m^2 and maximum BMI was 32kg/m^2 with mean and standard deviation was 28.37±2.29 kg/m^2. There were 33(53.2%) male patients and 29(46.8%) were female patients. SVR-12 was achieved in 51(82.3%) patients while SVR-12 was not achieved in 11(17.7%) patients. In present study by using chi-square test it was found that achievement of SVR-12 was not significantly associated with age group with *p*-value=0.748. Significant association was not found between the achievement of SVR-12 and gender with *p*-value=0.923. Significant association was not found between the achievement of SVR-12 and Duration of Dialysis and BMI having *p*-value=0.162 and *p*-value=0.847 respectively.

Table-I: Descriptive statistics (n=62)

	Minimum	Maximum	Mean	Std. Deviation
Age	15	60	36.52	14.03
Duration of Dialysis	3	10	6.71	1.81
BMI	25	32	28.37	2.29

Table-II: Distribution of gender

Gender	n(%)
Male	33(53.2)
Female	29(46.8)

Table-III: Response to treatment in terms of SVR12.

SVR-12	n(%)
Yes	51(82.3)
No	11(17.7)

Table-IV: SVR-12 With Respect to Age (n=62)

Presence of SVR-12				
Age	**Yes**	**No**	**Total**	***p*-value**
<45 Years	35	7	42	
>45 Years	16	4	20	
Total	51	11	62	

Chi-Square test applied

Table-V: SVR-12 With Respect to Gender (n=62)

Presence of SVR-12				
Gender	**Yes**	**No**	**Total**	***p*-value**
Male	27	6	33	
Female	24	5	29	
Total	51	11	62	

Chi-Square test applied

Table-VI: SVR-12 with Respect to Duration of Dialysis (n=62)

Presence of SVR-12				
Duration of Dialysis	**Yes**	**No**	**Total**	***p*-value**
<5 months	15	1	16	
>5 months	36	10	46	
Total	51	11	62	

Chi-Square test applied

Table-VII: SVR-12 with Respect to BMI (n=62)

Presence of SVR-12				
BMI	**Yes**	**No**	**Total**	***p*-value**
<28 Kg/m^2	17	4	21	
>28 Kg/m^2	34	7	41	
Total	51	11	62	

Chi-Square test applied

DISCUSSION

Sixty two cases were included by fulfilling the inclusion criteria by using non-probability consecutive sampling, it was observed that the minimum age was 15 years and maximum age was 60 years with mean and standard deviation of the age was 36.52±14.03 years. The minimum Duration of Dialysis was 3 months and maximum was 10 months. The minimum body mass index was found as 25kg/m^2 and maximum BMI was 32kg/m^2 with mean and standard deviation was 28.37 ±2.29 kg/m^2. There were 53.2% male patients and 46.8% were female patients. SVR-12 was achieved in 82.3% patients while SVR-12 was not achieved in 17.7% patients.

Previous study showed that twenty five patients (12 males) aged 35±22 (Mean±SD) years received sofosbuvir based therapy between December, 2015 and December, 2016. Eighteen patients had genotype 3, six had genotype I and one had genotype 4. Baseline RNA level was 6.40±057 log (Mean±SD). Five patients had imaging and endoscopic evidence of cirrhosis. Sixteen (64%) patients achieved sustained virological response (SVR12). Six patients achieved end of therapy response (ETR) and SVR12 is yet to be evaluated. Two patients were lost to follow up. One patient discontinued therapy due to development of extensive skin rash. Relapse was not seen in any of these patients and echocardiographic monitoring was not done.[11,12]

In present study by using chi-square test it was found that achievement of SVR-12 was not significantly associated with age group with *p*-value=0.748. Significant association was not found between the achieve-ment of SVR-12 and gender with *p*-value =0.923. Significant association was not found between the achieve-ment of SVR-12 and Duration of Dialysis and BMI having *p*-value=0.162 and *p*-value=0.847 respectively.

In a previous research, a total of 62 treatmentnaïve patients were included. Mean age was 33.3±10.2 years; 66% were men. Median number of copies were 10^6/dl. None had clinical evidence of cirrhosis. The most common genotype was genotype 1 in 64.5% of cases, followed by genotype 3 in 29% of cases. Thirtynine patients were treated with SOF every other day/ ribavirin, 2 patients with SOF daily/ribavirin, 6 with SOF every other day/daclatasvir, and 15 patients with SOF daily/daclatasvir. All patients were treated for 12 weeks. Fifty-nine (95.2%) patients had a sustained viral response (SVR). There was no impact of genotype on SVR. Twenty-three patients (37%) had complications while on therapy; 13(20.3%) had dyspepsia, 4 had tuberculosis, and 3 had bacterial pneumonia. Most of the patients 23(56%) in the ribavirin group required an increase in the erythropoietin dose. No patient discontinued therapy due to complications.[13]

Existing literature showed that sixteen patients (12 males) aged 45±12 years received sofosbuvirbased treatment. These patients were on hemodialysis from 10(2-48) months. Eleven of these patients had genotype 1, four had genotype 3, and one had genotype 4 infection; baseline RNA was 7 (5-8) log. The following treat-ment regimens were used: sofosbuvir, ribavirin, and low dose peginterferon (n=8; 6 genotype 1 and one each had genotype 3 and 4); sofosbuvir and daclatasvir (n=7); sofosbuvir, ribavirin, and daclatasvir (n=1). Ten patients achieved end of treatment response and 8 (80%) of these achieved sustained virological response at 12 weeks (SVR12); six are on treatment. Two patients with genotype one (including one with cirrhosis) had relapsed. Seven patients needed blood transfusion; interferon was stopped in one due to thrombocy-topenia. Fatigue was present in 4 patients.[14]

Patients with CKD have a higher prevalence of HCV infection compared to the general population. Recent studies suggest that HCV-infected patients with CKD have an accelerated rate of kidney function loss and an increased risk of progression to ESRD.[15] In one study by Sabry *et al*. showed that HCV-infected patients with CKD had an increased mortality and an accele-rated rate of progression to ESRD, raising the important question of whether treating to obtain a sustained

virological response defined as an undetectable viral load 12 weeks after completion of treatment (SVR12) would diminish the rate of decline in GFR.[16] Studies have consistently shown that HCV infection is associated with an increased mortality in patients with ESRD. In a meta-analysis by Hossein *et al.* the relative risk of mortality was 1.35(95% confidence interval, 1.25-1.47) among HCV-infected patients with ESRD.[17] Since the introduction of serological assays for the detection of HCV infection, several multi-center sur-veys exist, mostly based on serologic detection of HCV infection. On the basis of data of this body, prevalence rates have been shown to range between 1.4% and 28.3%.[18,19]

Effective screening of blood products virtually eliminated HCV transmission by blood transfusion more than two decades ago, and a subsequent decrease in HCV incidence in HD units in developed countries occurred. In Western Europe, large declines in the frequency of anti-HCV antibodies were noted during last ten years in several countries. As an example, the prevalence of anti-HCV antibody in Italy ranges now between 8-12% (down from around 30% in early 2010).[20,21]

CONCLUSION

After treatment with Sofosbuvir and daclatasvir among hepatitis C positive hemodialysis patients, Sus-tained virological response -12 was achieved in 51 (82.3%) patients while SVR-12 was not achieved in 11 (17.7%) patients. Effect modifiers like age, gender, dur-ation of dialysis % BMI did not show significant influence.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

QA: & IA: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

STS: Data acquisition, data analysis, approval of the final version to be published.

SA: Critical review, concept, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Butt N, Khan MA, Akbar A. Effectiveness of sofosbuvir and daclatasvir in treatment of hepatitis-C: An experience of tertiary care hospital in Karachi. Pak J Med Sci 2021; 37(7): 2014.
2. Ali I, Isram J. Success of (NS5B/NS5A Inhibitors) Sofosbuvir/ velpatasvir in management hepatitis C studied tertiary care hea-lthcare in Rawalpindi, Pakistan. 2018; 89(3): 321–331.
3. Alghamdi FS. Evaluation of patients' recovery from following antiviral treatment with dacla-tasvir and sofosbuvir in AL-Baha Region. Int J Advanc Human Res 2024; 4(1): 1-20.
4. Vyas BH, Darji NH, Rana DA, Vyas KY, Malhotra SD. Impact of newer direct-acting antiviral drugs based on quality-adjusted life years: A prospective pharmacoeconomic study in hepatitis C patients. Perspect Clin Res 2021; 12(2): 76.
5. Kamel S, Elessawy H, Ashraf O, Elbaz A, Dabbous H, El-Sayed M et al. Effectiveness of direct-acting antivirals in treatment of elderly Egyptian chronic hepatitis C patients. Gastroenterol Insights 2021; 12(3): 336-346.
6. Yunihastuti E, Hariyant o R, Sulaiman AS, Harimurti K. Hepa-titis C continuum of care: Experience of integrative hepatitis C treatment within a human immunodeficiency virus clinic in Indonesia. Plos one 2021; 16(8): e0256164.
7. Elhaddad A, Elhassi A. Sofosbuvir and daclatasvir in the treat-ment of chronic hepatitis c virus infection at Benghazi medical center: Our experience. Libyan J Med Sci 2019; 3(4): 119-124.
8. Mahmoud HS, Alemam MF. Safety and efficacy of ombitasvir, paritaprevirand ritonavir combination with ribavirin for treat-ment of chronic hepatitis C virus in advanced kidney diseases patients in upper Egypt. SVU-Int J Med Sci 2023; 6(1): 12-19.
9. Rossato G, Tovo CV, Almeida PR. Treatment of chronic hepatitis C in patients with chronic kidney disease with Sofosbuvir-basead regimes. Brazil J Infec Dis 2020; 24: 25-29.
10. Chugh Y, Premkumar M. Cost-effectiveness and budget impact analysis of facility-based screening and treatment of hepatitis C in Punjab state of India. BMJ open 2021; 11(2): e042280.
11. Ajlan AA, Ahmed M, Abu-Riash T, Alquaiz M, Alkhail FA, Alashgar H. Developing a multidisciplinary HCV direct-acting antivirals utilization management and assessment program. J Am Pharma Associ 2021; 61(2): e159-170.
12. Li C, Liang J, Xiang H, Chen H, Tian J. Effectiveness of direct-acting antivirals in maintenance hemodialysis patients compli-cated with chronic hepatitis C. Medicine 2020; 99(48): 10-15.
13. Ryu JE, Song MJ, Kim SH. Safety and effectiveness of direct-acting antivirals in patients with chronic hepatitis C and chronic kidney disease. Korean J Intern Med 2022; 37(5): 958-68.
14. Atsukawa M, Kondo C, Kawano T. Development of interferon-free, direct-acting antivirals treatment for Japanese patients with chronic hepatitis C infection and chronic kidney disease. J Nip Med School 2021; 88(3): 163-70.
15. Balk EM, Adam GP, Jadoul M, Martin P, Gordon CE. A Systematic Review of Direct-Acting Antivirals for Hepatitis C in Advanced Chronic Kidney Disease. Kid Int Rep 2022.
16. Sabry N, Kamel AM, Cordie A, Esmat G. Daclatasvir as a hepa-titis C infection treatment option: an up-to-date evaluation. Expert Opinion Pharmacother 2023; 24(2): 159-70.
17. Poustchi H, Majd Jabbari S, Merat S, Sharifi AH, Shayesteh AA, Shayesteh E. The combination of sofosbuvir and daclatasvir is effective and safe in treating patients with hepatitis C and severe renal impairment. J Gastroenterol Hepatol 2020; 35(9): 1590-4.
18. Elmelodi MB, Shaibani B, Ayad K. Elbasvir/grazoprevir treatment in a hemodialysis patient with hepatitis C Virus Genotype 2a Infection, not responded to sofosbuvir/daclatasvir combination therapy. Libyan J Med Sci 2021; 5(3): 132-134.
19. Li PK, Bavanandan S, Mohamed R, Szeto CC. 2018 kidney disease: Improving global outcomes (KDIGO) hepatitis C in chronic kidney disease guideline implementation: Asia summit conference report. Kidney Int Rep 2020; 5(8): 1129-1138.
20. Debzi N, Berkane S, Manouni C, Amani N, Hemmam S. Efficacy of Sofosbuvir/Daclatasvir in a Single Tablet for Treating Chronic Viral Hepatitis C. J Clin Pharm Therap 2023; 2023.
21. Taneja S, Duseja A, Mehta M, De A, Verma N, Premkumar 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(4): 705-709.