Original Article

One Year Mortality & Reinfection Rate of Hepatitis C Among Patients on Hemodialysis after Successful Direct-Acting Antiviral Treatment

Sidra Shafiq Cheema[1], Ambreen Tauseef[1], Manal Fatima[1], Marium Danish Iqbal[1], Sana Khurshid[2] and Shafiq ur Rehman Cheema[2]

ABSTRACT

Objective: The key goal of this research is to evaluate the incidence of HCV reinfection among patients undergoing maintenance hemodialysis (MHD) after achieving successful treatment for hepatitis C.

Study Design: A prospective randomized interventional trial study

Place and Duration of Study: This study was conducted at the Jinnah Hospital dialysis center from January 2021 till December 2022.

Materials and Methods: We led a prospective randomized interventional trial at Jinnah Hospital dialysis center, analyzing data from a group of patients undergoing MHD who had previously received direct acting antivirals (DAA) therapy for HCV treatment. Following successful therapy with DAA and accomplishment of sustained virologic response (SVR), these patients were monitored for one year. During this period, strict adherence to "universal precautions" was implemented to prevent cross-contamination of HCV. HCV RNA PCR measurements were taken at the one-year mark to assess reinfection, defined as a positive HCV RNA measurement after SVR. In cases where reinfection was detected, genotyping was performed. We calculated the raw rates of reinfection per 100 person-years as a measure of reinfection incidence. Additionally, as a secondary objective, we calculated the one-year mortality rate within this treated population.

Results: Among the cohort of patients treated with DAAs, none of the patients in group 1 experienced reinfection one year after achieving SVR. However, in group 2, two out of 14 patients were identified with reinfection, and the genotype of the reinfection matched their previous genotype. The overall reinfection rate in the entire cohort was 2 out of 32 patients, amounting to 6.25%. The crude reinfection rate was calculated to be 6.25 per 100 person-years. Furthermore, the one-year mortality rate was determined to be 16% in group 1 and 44% in group 2.

Conclusion: The rate of reinfection among patients on maintenance hemodialysis who have been successfully treated for HCV is low when strict implementation and compliance to "universal precautions" are practiced.

Key Words: Mortality & Reinfection Rate, Hepatitis C, Hemodialysis, Direct-acting antiviral Treatment.

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INTRODUCTION

Hepatitis C virus (HCV) infection poses a significant global health and economic challenge, particularly among individuals undergoing hemodialysis.

[1.] Department of Nephrology, CMH Lahore medical college & IOD.
[2.] Department of Nephrology, Jinnah hospital & Allama Iqbal Medical College, Lahore.

Correspondence: Dr. Shafiq Cheema, Professor of Nephrology, Allama Iqbal Medical College ~ Jinnah Hospital, Lahore.
Contact No: 0311-238-1111
Email: shafiqcheema@yahoo.com

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Outbreaks and cross-infections of HCV within hemodialysis units have been well-documented[1-2], with previous studies revealing HCV prevalence ranging from 2.6% to 60% among hemodialysis patients, which is substantially higher compared to the general population[3-5]. The danger of HCV transmission within hemodialysis centers has decreased over time because of advancements in testing and infection control measures.[6,7]

Chronic hepatitis C infection in patients on continued dialysis is associated with a greater overall mortality risk[8,9], as well as a potential link to the development of renal cell carcinoma[10] and an elevated risk of severe infections in recipients of renal transplantation[11]. Treatment options for Hepatitis C Virus in dialysis patients have traditionally involved pegylated-interferon alone or in combination with ribavirin, which are related with longer treatment durations, poor virologic response rates, limited tolerability, a high

occurrence of adverse effects, and necessitate close supportive care.[12]

The advent of direct-acting antiviral agents (DAAs) has revolutionized the treatment landscape for individuals with HCV and chronic renal impairment[13], offering improved efficacy, tolerability, and safety compared to previous regimens. DAAs, such as the combination of the NS5B inhibitor sofosbuvir (SOF) and the NS5A inhibitor daclatasvir (DCV), with or without ribavirin (RBV), have demonstrated high effectiveness and tolerability in treating HCV infection in patients undergoing maintenance dialysis.

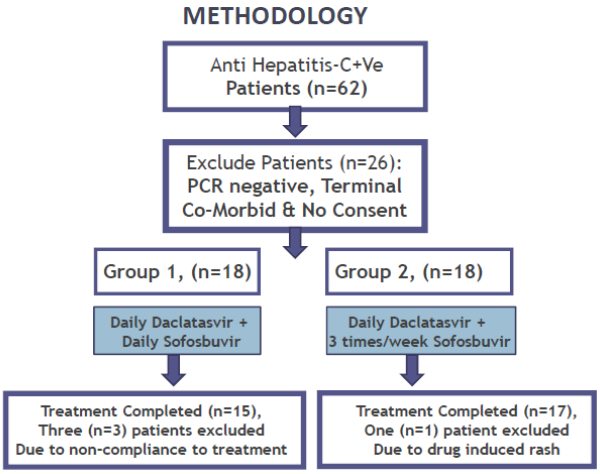
Given the adverse effect of Hepatitis C Virus infection on morbidity and in dialysis patients, effective treatment is of paramount importance. However, reinfection poses a potential barrier to achieving HCV elimination goals in this high-risk population. In hemodialysis facilities, lapses in healthcare quality, including dialysis system contamination, inadequate disinfection of environmental surfaces, inappropriate contact between healthcare staff and equipment/ patients, and mishandling of parenteral drugs, are common challenges.[14-16]

Therefore, this study aims to evaluate reinfection rates following successful treatment with DAAs in the hemodialysis population, with a focus on strict adherence to infection control practices. By assessing reinfection rates, we can better understand the impact of these measures on preventing HCV reinfection and advancing the goal of HCV elimination in this high-risk population.

MATERIALS AND METHODS

Trial Design and Participants: Data from the aforementioned cohort, consisting of 36 patients, who underwent DAA therapy for hepatitis C treatment in a prospective randomized interventional trial, were analyzed. In this trial, group 1 (18 patients) were given a daily dosage of 400 mg sofosbuvir and 60 mg daclatasvir, whereas group 2 (18 patients) were given 400 mg sofosbuvir thrice a week and 60 mg daclatasvir daily for a duration of 12 weeks. Patients with compensated cirrhosis were treated for 24 weeks, as indicated in the figure. This Study was conducted in from January 2021 till December 2022 for a period of 02 years.

Outcomes and Follow Up: After attaining SVR, the 32 treated patients were monitored for a period of one year. Throughout this duration, strict compliance to "universal precautions" was maintained to prevent the cross-contamination of HCV. HCV RNA PCR testing was conducted again at the one-year mark. Reinfection, in the context of this study, was defined as a positive HCV RNA measurement at 1 year following the attainment of SVR. In order to distinguish between reinfection and cross-over infection, genotyping was performed for patients who tested positive for HCV RNA through PCR. Raw reinfection rates per 100 person years were subsequently calculated. As a secondary objective, the one-year mortality rate within this treated population was also determined.



RESULTS

Among the 32 treated patients, none of the individuals in group 1 experienced reinfection one year after achieving SVR. However, in group 2, consisting of 14 patients, two cases of reinfection were identified, with the same genotype as the previous infection. The SVR after one year of treatment completion was 100% in group 1 (daily sofosbuvir and daclatasvir), while it was 85.8% in group 2 (daily daclatasvir and thrice weekly sofosbuvir). The overall SVR rate across both groups was 86.3%. The reinfection rate for the entire cohort was 2 out of 32 patients (6.25%). Calculating the crude reinfection rate yielded 6.25 cases per 100 person years. The 1-year mortality rate was 16% in group 1, 44% in group 2, and an overall mortality rate of 30% (Table 1 and Figure 1 & 2.)

Table No. 1: Baseline Characteristics of Patients in each treatment group

Variables n=36	**Group 1 n=18**	**Group 2 n=18**	**P-Valu**
	Mean ± SD	**Mean ± SD**	
Age (Years)	**47.22±14.17**	**53.89±14.11**	0.17
Duration of Known Hepatitis C (Years)	4.61±3.84	3.55±1.92	0.31
Duration of Dialysis (Years)	4.23±2.63	5.33±2.79	0.23
HCV RNA PCR (log 10 IU/ml)	5.88 ± 6.0	6.16 ± 6.58	0.46
Genotype 1 Patients	N= 06	N= 06	——
Genotype 2 Patients	N= 00	N= 01	——
Genotype 3 Patients	N= 12	N= 11	——
Cirrhosis	N=04	N=06	___
Treatment	N = 03	N = 02	___

Experienced			
Treatment Withdrawal	N = 03	N = 01	——
Aspartate Amino-transferase (U/L)	57.06±48.71	34.5±25.27	0.09
Alanine Amino-transferase (U/L)	50.89±44.08	40.50±34.86	0.44
Hemoglobin (g/dl)	10.53±1.61	11.51±1.15	0.04
White Blood Cells x10^3/mm3	6.33±1.93	6.44±1.91	0.87
Platelets x10^3/mm3	163.27±65.34	175.44±40.11	0.51

Independent t-test was used to assess the significance

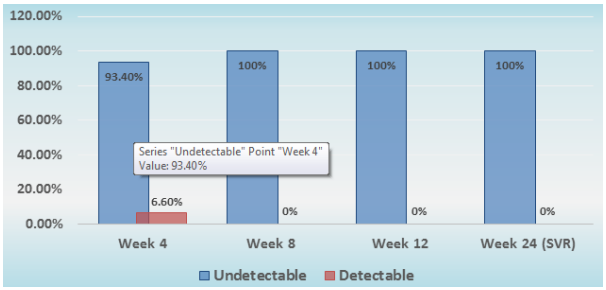


Figure No. 2: Undetectable Viral load in Group 1 Patients

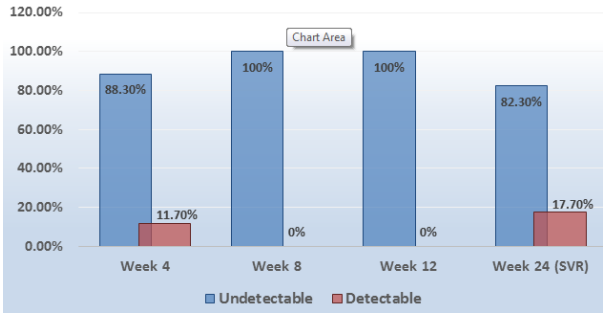


Figure No. 3: Undetectable Viral load in Group 2 Patients

DISCUSSION

Pakistan, HCV is prevalent, with approximately 6.8% of the population potentially infected, representing a significant forty percent increase in HCV prevalence amongst the common populace in recent years.[18] Despite this, newer medications have shown a high SVR rate, even in populations traditionally considered difficult to treat. Unfortunately, these newer DAAs that are not dangerous for patients with advanced chronic kidney disease (CKD) are not yet available in Pakistan, further limiting treatment options. Additionally, the majority of patients in Pakistan (about 80-90%) are infected with genotype 3, which adds to the complexity of treatment options.[17]

Sofosbuvir (SOF)-based regimens are currently the backbone of treatment for HCV, and the combination of once daily oral daclatasvir plus sofosbuvir has shown high rates of SVR in hemodialysis patients infected with HCV genotypes 1, 2, or 3.[18,19] This study, which serves as background information, is the largest study conducted in Pakistan to date, demonstrating the harmless and efficient utliziation of SOF-based therapy in treating HCV in patients undergoing maintenance hemodialysis. It also represents the first follow-up study to investigate reinfection in this high-risk population.

Reinfection with HCV is a specific apprehension in patients who remain involved in dangerous and highly risky behaviors like injection drug use and those co-infected with HIV/HCV.[20,21] Hemodialysis patients are also considered a high-risk population. Researches have addressed Hepatitis C Virus reinfection after treatment-induced clearance amongst patients who inject drugs. As an example, in Vancouver, the incidence of initial Hepatitis C Virus infection was 7.3 cases per 100 person years, and the risk of reinfection following HCV treatment was 3.2 cases per 100 person years.[22] In Amsterdam, the local incidence of initial Hepatitics C Virus infection was 0.35 cases per 100 person years, expressively less than in Vancouver, and the risk of reinfection after HCV treatment was 0.76 cases per 100 person years.[23] Another study in Australia showed that the incidence of potential HCV reinfection amongst people with clearance of Hepatitis C Virus was 42 per 100 person years (95% CI, 25-61/100 PY), similar to the incidence of intital HCV infection amongst participants negative for HCV.[24]

In a study from Spain, which looked at 118 prisoners (81% injection drug users) treated for HCV and who had attained SVR between 2003 and 2009,[25] a high incidence of reinfection was observed, particularly amongst those who were ongoing injection drug users.[26] Among the participants, HCV reinfection was identified in 9 former injection drug users, with 7 experiencing a switch in HCV genotype, resulting in a total reinfection rate of 5.27 cases per 100 person years. The incidence of reinfection was significantly higher amongst active drug users (hazard ratio HR = 12.47; 95% CI: 2.90-53.71), HIV co-infected individuals (HR = 9.95; 95% CI: 1.73-57.34), and those involved in multiple risk behaviors after treatment (HR = 7.47; 95% CI: 1.19-46.89). A meta-analysis of these studies concluded that HCV mono-infected patients without recognized risk factors had a pooled estimate of reinfection rate and summary 5 year reinfection risk of zero. In HCV mono-infected patients involved in highly risky activities, the pooled reinfection rate was 19.06/1000 person-years (95% CI, 11.42-28.16), resulting in a summary 5-year risk of 10.67% (95% CI, 6.38%-15.66%). In HIV/HCV co-infected patients, the pooled reinfection rate was 32.02/1000 person years (95% CI, 0.00-123.49), leading to a summary 5 year risk of 15.02% (95% CI, 0.00%-48.26%). The review concluded that most patients continue to have a SVR (i.e., no reinfection) 5

years after treatment. The higher reinfection risk among people engaged in higher risk activities and those with HIV-HCV co-infection underscores the need for prevention campaigns particularly targeted at these groups. Similarly, in our study, the pooled reinfection rate in HCV mono-infected patients on hemodialysis was 2/32 (6.25%), comparable to other high-risk populations, with a crude reinfection rate per person-year of 0.0624. Therefore, the focus should be on prevention strategies.

Dialysis centers have a duty to guarantee the strict implementation of infection-control protocols to stop the nosocomial transmission of blood-borne pathogens, including HCV, between patients under their care, whether through direct contact or via contaminated appliances or surfaces. The National Kidney Foundation recommends that hemodialysis unit design should enable the easy implementation of infection control strategies. Sufficient time between shifts should be provided to allow effective decontamination of equipment and surfaces, and ease of disinfection should be considered when choosing new equipment. It is crucial to maintain infection prevention staff training and vigilance during changes in staff-to-patient ratios or when employing new staff. Regular risk evaluations should be carried out, and measures to diminish or eliminate risks should be developed. Isolating HCV infected patients as an alternative to strict infection control procedures for preventing the spread of blood borne pathogens is not recommended by the National Kidney Foundation. Moreover, using assigned dialysis machines for HCV-infected patients is also not endorsed (moderate evidence).

CONCLUSION

When strict implementation, application, and unwavering compliance to "universal precautions" is practiced, the reinfection rate among successfully treated HCV patients on maintenance hemodialysis is low. This means that HCV RNA-negative patients can safely undergo dialysis in the same unit as HCV RNA-positive patients, and there is no need for dedicated machines for HCV-negative patients.

However, despite successful HCV treatment, mortality remains high in this cohort. This finding is consistent with several meta-analyses that have concluded that HCV is an independent and significant risk factor for death in end stage renal disease (ESRD) patients undergoing dialysis. It underscores the importance of addressing HCV infection and its associated complications in the management of ESRD patients on dialysis to improve overall patient outcomes.

Author's Contribution:

Concept & Design of Study:	Sidra Shafiq Cheema
Drafting:	Ambreen Tauseef, Manal Fatima
Data Analysis:	Marium Danish Iqbal, Sana Khurshid, Shafiq ur Rehman Cheema
Revisiting Critically:	Sidra Shafiq Cheema, Ambreen Tauseef
Final Approval of version:	Sidra Shafiq Cheema

Conflict of Interest: The study has no conflict of interest to declare by any author.

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