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Incidence of hepatitis C recurrence after kidney transplantation and response to direct-acting antiviral therapy: A multi center study

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***Abstract*---**Aim: The purpose of this study is to investigate the efficacy and graft survival of direct antiviral agents in Hepatitis C-positive renal transplant recipients. Design: A Multi center study. Duration & place of study: From February 2020 to February 2021, a cohort of Hepatitis C positive Renal Transplant Recipients will participate in a study at the Saidu teachnig hospital Swat and ikd peshawar. Methodology: the study conducted in STH and IKD peshawar Patients with hepatitis C who have received a kidney transplant will be chosen if they meet the inclusion and exclusion criteria, and then they will be followed for three months after startingthe direct acting antiviral (DAA) treatment. Result: With a mean age of 35.01±11.6 years, the study's 100 participants were evenly split between sexes (62% male). The treatment for HCV was a [100%] success. Throughout the course of therapy (ranging from 6-12 weeks), there was no discernible shift in the mean values of total bilirubin, haemoglobin, platelet count, serum creatinine, or estimated glomerular filtration rate. ALP levels

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decreased considerably across all time points of follow-up, whereas ALT and AST levels decreased rapidly over the first 4 weeks and thereafter stabilised. From week 0 through week 12, albumin levels were stable from their initial baseline values, but jumped by a large margin at week 6. From the beginning of the trial until the conclusion, both the white blood cell count and the blood glucose level decreased dramatically. Among the 58 people who had a [eGFR >91] at baseline, a comparison at week 12 revealed that 14 (21%) had an eGFR between 58 and 91, and 6 (11%) had an eGFR of 11 or less (29 – 61). Conclusion: Transplant recipients who have HCV have a significantly higher chance of having their graft fail. DAA treatment was found to be effective in curing HCV infection in kidney transplant recipients, leading to marked improvements in liver function and no loss of allograft function, as was observed in our study.

***Keywords*---**topical antiviral agents, sustained antiviral therapy response, hepatitis C.

Introduction

Hemodialysis patients with Chronic Kidney Disease have a high prevalence of Hepatitis C (HCV) infection. Due to the immunomodulatory effects of HCV, the persistence of HCV infection in renal transplant recipients on immunosuppression regimens increased the risk of allograft rejection, new onset diabetes, cardiovascular complications, de novo post-transplant glomerular diseases, infection, and liver fibrosis[1]. Interferon medication is suggested for non-CKD patients, however it is contraindicated in post renal transplant patients due to the increased risk of acute rejection[2,3]. Other antiviral regimens, such as ribavirin and amantadine, taken alone or in combination, were ineffective in reducing HCV virus load[4,5].

Direct acting antiviral medications (DAA) are very efficient in eradicating HCV infection in cirrhotic and non-cirrhotic patients, liver transplant recipients, and combined liver and kidney transplant recipients[6]. Different trials using sofosbuvir-based regimens in conjunction with ribavirin or other DAAs such as daclatasvir, simeprevir, and ledipasvir in liver transplant patients have shown 80 to 90 percent viral clearance.[7].Sofosbuvir in combination with other DAAs with or without ribavirin shown excellent viral clearance in kidney transplant patients; nevertheless, in this trial, researchers discovered a drop in CNI level in renal transplant recipients on triple immunosuppression[8]. By administering sofosbuvir and ledipasvir19 to HCV- infected post-kidney-transplant patients, a second research demonstrates good outcomes.In this trial, we prospectively examined the efficacy of a combination of sofosbuvir and daclatasvir-based antiviral regimens for the treatment of HCV PCR-positive patients of kidney transplants[9,10].

Materials and Methods

The study included renal transplant patients with persistent HCV infection of all genotypes. Patients with relapse of HCV infection previously treated with anti-

viral therapy, as well as those who underwent renal transplant without receiving any anti-viral regimens, have stable graft function with an estimated glomerular filtration rate (e GFR) greater than 36 ml/min per 01.72 m2 and are on any induction and immunosuppression regimen.Excluded from the research were renal transplant patients with any of the following diseases or features. Coinfection with chronic Hepatitis B or HIV infection, acute or chronic rejection prior to initiation of DAAs,Hemoglobin (Hb) less than 8 g/dl, neutrophils less than [1500/ml], platelets less than [74,000/ml], direct bilirubin [>03xULN, ALT and AST> 5x upper limit of normal (ULN), albumin]; Hemoglobin (Hb) less than g/dl prior to the commencement of DAAs. Any transfusion of blood within four weeks.

The key outcome measure was sustained virological response (SVR) at week 12 after the initiation of DAAs. SVR was defined as an undetectable HCV RNA PCR in a prior quantifiable or detectable HCV PCR-positive individual. Before initiating DAAs, the fibrosis state of the liver was assessed by transient elastography as measured by Fibro scan.At baseline, 4 weeks, 8 weeks, and 12 weeks, we assessed Complete blood count (CBC), renal function, Liver function including serum albumin, serum glucose level, proteinuria (protein to creatine ratio in spot urine sample), and levels of immunosuppressive drug. As antiviral medication, all kidney transplant patients received a combination of [sofosbuvir 400 mg] and [daclatasvir 60 mg] for twelve weeks.

Results

HCV treatment was [100%] effective among 100 post-kidney-transplant patients. They had a mean age of 35.0111.6 years, and 62 (62%) of them were men while the remainder were women. Initial viral load was 512876 copies. The average time required after transplant to begin HCV therapy was 4.1-0.06 months. Chronic GN was the leading reason of transplantation in 32% of cases, followed by renal atrophy and diabetes in 22% and 15% of cases, respectively. Prior to receiving an interferon transplant, two of the patients had had therapy six and fifteen years earlier. In the majority of instances (40%), the HLA match was 3/6, while just 14 (14%) cases had a match of 6/6. ATG induction was conducted in 16 (16%) patients, whereas 72 (76%) did not undergo induction. The majority of 92 (92%) patients were on Tacrolimus, while the remainder are on Cyclosporin. The most widespread genotype was 32percent chose 3a, then 26% and 18% chose 1a. Beforeresearch, 52% had grade F1 fibrosis, 8% were NODAT, and 24% had proteinuria (Table 1).

Total bilirubin levels, haemoglobin, platelet count, serum creatinine, and eGFR did not change significantly throughout 12 weeks of therapy and monitoring. ALT and AST levels decreased in the first 4 weeks and remained low, but ALP levels decreased at all follow-up intervals. Albumin levels rose at week 8 and remained steady at week 12. WBC count and blood glucose levels decreased from baseline to study conclusion (Table 2).Post-transplant, 29 (58.0%) had eGFR over 90, 20 had between 60 and 90, and 1 had between 30 and 60. At 4 weeks, 12 patients' eGFR dropped, 5 improved, and 33 remained stable. This 4th week movement across groups was minor.0.107. At 8 weeks, 13 had reduced kidney function and 6 had improved, although the p-value was 0.072. Comparing 12th week to baseline, 7 (24.1%) of 29 with eGFR >90 at baseline had eGFR 60–90 and 3 (10.3%) had

eGFR even less (30–60). 30% of individuals with eGFR 60–90 at baseline improved to >90, whereas 25% deteriorated to 30–60. The decrease in renal function with therapy was significant after 12 weeks compared to baseline (p=0.044) (Table 3).Similar increases in proteinuria between baseline and follow-up had p-values of 0.406, 0.306, and 0.416 at weeks 4, 8, and 12. 3 of 12 people with proteinuria at baseline recovered entirely, while 1 of 38 without proteinuria acquired it. (table.01 to 03)

Table 1: significant features of kidney transplant recipients

		[Count]	[%]
[Cause of ESRD]	[Chronic GN]	34	34.0
	[b/l shruken kidney]	22	22.0
	[Diabetes]	16	16.0
	[Nephrolithiasis]	12	12.0
	[CIN]	6	6.0
	[Pstpartum AKI]	4	4.0
	[Vu reflex]	4	4.0
	[polycystic kidney]	2	2.0
[Previous HCV Tx Pre transplant]	[IFN 7 year back]	2	2.0
	[IFN 10 year back]	2	2.0
	[No]	100	96.0
[HLA match (x/6)]	[01.00]	10	10.0
	[02.00]	14	14.0
	[03.00]	44	42.0
	[04.00]	18	18.0
	[05.00]	2	2.0
	[06.00]	14	14.0
[Induction]	[ATG]	16	16.0
	[Basiliximab]	8	8.0
	[No]	98	76.0
[Immunosuppressive regimens(Y/mmf/delt)]	[Cyclo]	16	8.0
	[Tac]	92	92.0
[HCV genotype]	[3a]	32	32.0
	[03]	26	26.0
	[01a]	18	18.0
	[01]	10	10.0
	[02]	8	8.0
	[1 and 2]	4	4.0
	[1 and 3]	2	2.0
[Fibroscan]	[F0]	8	8.0
	[F1]	52	52.0
	[F2]	30	30.0
	[F3]	10	10.0
[NODAT]	[Yes]	8	8.0
	[No]	92	92.0
[proteinuria (mg/g creatinine Baseline]	[Nil]	78	76.0
	[≤ 0.4]	14	14.0

	[0.41 – 0.6]	8	8.0
	[> 0.6]	2	2.0

Table 2: Normalized biomarker values at four time points and inter-point comparison

[Bio-markers]	[Starting]			[04 week]	[08 week]		[12] week		[p-value]
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
[Bilirubin total mg/dl]	0.7	0.02	0.8	0.2	0.8	0.2	0.8	0.2	0.455
[ALT U/L]	37	16	28	7.2	29.3	8.1	29.1	7.6	0.026
[AST U/L]	33	12	31	9.7	31.8	8.2	31.4	7.8	0.021
[ALP U/L]	146	55	120	36.6	114.3	36.2	107.4	34.9	<0. 002
[s/albumin g/dl]	4	0.5	03	0.3	3.4	0.3	3.4	0.3	0.003
[Hemoglobin g/dl]	12	02	12	2.4	11.6	2.4	11.6	2.5	0.661
[WBC count]	11	03	10	2.9	9.3	2.8	9.1	2.9	0.005
[Platelet count]	229	52	231	66.5	239.0	78.1	243.2	81.9	0.816
[[s/creatine mg/dl]	2	0.3	01	0.3	1.0	0.3	1.0	0.3	0.565
[[e GFR ml/min per 1.73 m]	96	22.6	94	27.0	91.8	24.7	90.5	27.0	0.466
[BSL mg/dl]	101	30.6	98	21.8	93.0	14.8	89.6	10.7	0.008

Table 3: Renal function classification shift over time versus at baseline

Time				Baselin		e			
eGFR (ml/min per 1.73 m)		[> 91]		[61 – 91]		[31 – 61]		[Total]	
		Count	%	Count	%	Count	%	Count	%
[Week – 04]	> 90	21	72.4	5	25.0	0	0.0	26	52.0
	60 – 90	6	20.7	11	55.0	0	0.0	17	34.0
	30 – 60	2	6.9	4	20.0	1	100.0	7	14.0
	Total	29	100.0	20	100.0	1	100.0	50	100.0
[McNemar = 6.09]				P-value = 0.107					
[Week – 08]	> 90	20	69.0	6	30.0	0	0.0	26	52.0
	60 – 90	6	20.7	10	50.0	0	0.0	16	32.0
	30 – 60	3	10.3	4	20.0	1	100.0	8	16.0
	Total	29	100.0	20	100.0	1	100.0	50	100.0
McNemar = 7.00				P-value = 0.072					
[Week – 12]	> 90	19	65.5	6	30.0	0	0.0	25	50.0
	60 – 90	7	24.1	9	45.0	0	0.0	16	32.0
	30 – 60	3	10.3	5	25.0	1	100.0	9	18.0

	Total	29	100.0	20	100.0	1	100.0	50	100.0
[McNemar = 6.06]				P-valu	e = 0.041				

Discussion

Chronic allograft rejection, transplant glomerulopathy, HCV-associated glomerulonephritis, and post- transplant hyperglycemia all contribute to early graft loss in HCV-positive renal transplant patients. As compared to the non-HCV positive renal transplant population[11,12].these patients have a lower chance of surviving the first year after receiving a new organ and are more likely to experience death or serious illness as a result of cardiovascular problems, infections, or liver disease[13]. A new meta-analysis comprising 130,320 transplant patients demonstrates the detrimental impact of HCV on kidney transplant outcomes. They found that HCV-positive patients had a 76% higher risk of graft loss and an 85% higher risk of all-cause death compared to HCV-negative recipients[14].

Our research population had an SVR of 100% after 12 weeks of DAA therapy, which is on line with other studies. Similarly, Lubetzky et al[15].23 found that after 12 weeks of therapy, SVR was at 100%. After 12 weeks of DAA therapy, Beinhardt et al.24 likewise found 95% SVR. All 114 kidney transplant patients with HCV infection and an eGFR of 40mL/min or above who participated in the trial by Colombo et al.26 achieved SVR after 12 weeks of therapy[16].After taking DAA, liver function increased dramatically. After starting Treatment, there was a notable drop in levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Similar results were also found by Kamar et in his research and by Sawinski et al. [17].

We detected no significant difference in allograft function (eGFR and serum creatine) between before and after DAA treatment. Furthermore, we identified no acute rejection event or graft loss with DAA therapy. There was no discernible improvement in proteinuria while on therapy. Similar results were found by Eisenberger et al. But there are caveats to our research. As a single-center study, the sample size was limited[18].

Conclusion

It is generally known that a patient who has had a kidney transplant has an increased chance of getting HCV. According to our study, treatment with DAAs was successful in eliminating HCV infection in kidney transplant patients. This resulted in considerable improvements in liver function, and there was no loss of allograft function.

Conflict of Interest: None of authors have any conflicts of interest to declare
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