DOI: https://doi.org/10.53350/pjmhs22163134

ORIGINAL ARTICLE

Effects and outcome of Direct Acting Antiviral Therapy for Eradication of Hepatitis C in Kidney Transplant patients

AHMED AYYAZ, AZHAR ALI KHAN, NASIR IBRAHIM, SEHRISH SARWAR, AZHAR WAHEED KHAN, HAFIZ HAMAD ASHRAF
Kidney Transplant Unit, Sh. Zayed Hospital, Lahore
Correspondence to Dr. Hafiz Hamad Ashraf, Email: hafizhamadashraf@gmail.com

ABSTRACT

Aim: To look for effects and graft outcome of Direct Antiviral Agents on Hepatitis C positive Renal Transplant Patients
Design: Prospective study
Duration & place of study: The study will be conducted in Shaikh Zayed Hospital's Kidney Transplant Unit, Lahore, and will comprises of consecutive Hepatitis C positive Renal Transplant Recipients from January 2018 to January 2020
Methodology: The Hepatitis C Positive Renal Transplant Recipients will be selected after fulfilling Inclusion and Exclusion Criteria and we will follow the patient for 3 months after initiation of DAA regime.
Result: The study included 50 patients average age was 36.1±10.5 years and 32(64%) of them were male and rest were females. Therapy for HCV was 100.0% successful. The total bilirubin levels, hemoglobin, platelet count, serum creatinine and eGFR had no significant change in averages over 12 weeks of treatment. The ALT and AST levels reduced significantly in first 4-week time and then stayed at a level while the ALP levels reduced significantly over all intervals of follow-ups. The albumin levels increased significantly at week 8 and stayed unchanged on week 12 as compared to baseline. The WBC count and blood glucose levels reduced significantly from baseline till end of study. 12th week was compared with baseline, it was observed that among 29 with eGFR >90 at baseline 7(24.1%) had eGFR 60 – 90 and 3(10.3%) had eGFR even less (30 – 60).
Conclusion: HCV is a well-recognised risk factor of poor graft survival in kidney transplant patients.
In our study it was observed that DAA treatment can resolved HCV infection in kidney Transplant Recipients with significant improvement of liver function without loss of allograft function.
Keywords: Hepatitis C, Direct Antiviral Agents, Sustained Virological Response

INTRODUCTION

Hepatitis C (HCV) infection in Chronic Kidney disease patients on hemodialysis is very common. The persistent of HCV infection in Renal transplant recipients on immunosuppression regimes increased the risk of allograft rejection, new onset diabetes mellitus, cardiovascular complications, de novo post-transplant glomerular diseases, infection and liver fibrosis due to immunomodulatory effects of HCV[1-3]. Interferon therapy is recommended mode of treatment in non-CKD patients, but in kidney transplant patients it is associated with increased risk acute rejection that is why it is contraindicated in post renal transplant patients[4,5,6]. Other anti-viral regimes like ribavirin, amantadine either prescribed as monotherapy or in combination did not had any beneficial effect in lowering HCV viral load[7,8,9].

Direct acting antiviral agents (DAA) is very effective in eradicating HCV infection in cirrhotic and non-cirrhotic patients, liver transplant recipients and also in combined liver and kidney transplant recipients[10-15]. Different studies on sofosbuvir based regime in combination with either ribavirin or with other DAA such as daclatasvir, simeprevir and ledipasvir in patients having liver transplant result in virus clearance of 80 to 90 %[16,17].

Sofosbuvir in combination with other DAAs with or without ribavirin in Kidney transplant recipients had shown effective virus clearance, but in this study, researcher have found there was decreased in CNI level in renal transplant recipient on triple immunosuppression[18]. Another study gets successful result by treating HCV infection positive post renal transplant recipient with sofosbuvir and ledipasvir[19].

In our study, we prospectively analyzed the effect of combination of sofosbuvir and daclatasvir based anti-viral regime for treatment of HCV PCR positive kidney transplant recipients and their effects.

MATERIALS AND METHODS

Renal transplant recipients were included in study with chronic HCV infection with all genotypes. Patients having relapse of HCV infection previously treated with anti-viral therapy as well as those who underwent renal transplant without receiving any anti-viral regimes, with stable graft function with an estimated glomerular filtration rate (e GFR) higher than 35 ml/min per 1.73 m^2, with any induction regime and are on any immunosuppression regime.

Renal transplant patients with any of the following conditions or characteristics were excluded from study. 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 75,000/ml, direct bilirubin >3^{x}ULN, ALT and AST> 5^x upper limit of normal (ULN), albumin < 3.0 g/dl prior to initiation of DAAs. Any blood transfusion within 4 weeks.

The primary outcome was sustained virological response (SVR) at week 12 after starting DAAs. SVR was defined as undetectable HCV RNA PCR in study participant with previous quantifiable or detectable HCV PCR. Transient elastography as measured with Fibro scan was used before initiation of DAAs to determined liver fibrosis status.

We measured Complete blood count (CBC), renal function, Liver function including serum albumin, serum glucose level, proteinuria (protein to creatine ratio in spot urine sample), as well as levels of immunosuppressive medication at baseline, at 4 weeks, 8 weeks and then12 weeks.

All renal transplant patients received combination of sofosbuvir 400mg daily dose and daclatasvir 60mg daily dose for 12 weeks as an anti-viral therapy.

RESULTS

Among 50 post renal transplant patients, therapy for HCV was 100.0% successful. There average age was 36.1±10.5 years and 32(64.0%) of them were male and rest were females. The initial viral load was 501985±1011043. The average time after transplant, taken to start for the HCV treatment was 4.0±1.4 months.

The most common cause for transplant was Chronic GN in 34.0%, followed by shrunken kidney and Diabetes in 22% and 16.0% respectively. Two of them had previous treatment history, 7 and 10 years before transplant with interferon. The HLA match was 3/6 for most (42%) of the cases while only 7(14%) had 6/6 HLA match. ATG induction was performed in 8(16%) and 38(76.0%) had no induction. Mostly 46(92%) had Tacrolimus as treatment while remaining were on Cyclosporin. The most common genotype

Received on 21-09-2021
Accepted on 27-02-2022

was 3a in 32% followed by 3 and 1a in 26% and 18% respectively. Majority (52%) had fibrosis of grade F1, while 4(8%) of them were labeled as NODAT and 12(24%) had proteinuria before start of study (Table 1).

The comparison of various biomarkers explaining status of kidney and liver were also made between various follow-up times and it was noted that the total bilirubin levels, hemoglobin, platelet count, serum creatinine and eGFR had no significant change in averages over 12 weeks of treatment and observation period. The ALT and AST levels reduced significantly in first 4-week time and then stayed at a level while the ALP levels reduced significantly over all intervals of follow-ups. The albumin levels increased significantly at week 8 and stayed unchanged on week 12 as compared to baseline. The WBC count and blood glucose levels reduced significantly from baseline till end of study (Table 2).

When the category of kidney functions was described in ranges it was noted that post-transplant 29(58.0%) had eGFR above 90, and 20 had in the range of 60 – 90, while 1 had between 30-60. At 4th week 12 had a declined eGFR while 5 improved their category and 33 had unchanged category of eGFR. This shift between categories at 4th week was insignificant with p-value 0.107. At 8th week, there were 13 who had decreased kidney function and 6 had improved but still this shift between categories was insignificant with p-value 0.072. When 12th week was compared with baseline, it was observed that among 29 with eGFR >90 at baseline 7(24.1%) had eGFR 60–90 and 3(10.3%) had eGFR even less (30–60). Among those with eGFR 60–90 at baseline 6(30.0%) improved to >90 and 5(25.0%) worsened to 30–60. The shift of cases at 12th week as compared to baseline suggested that the change in renal function during treatment time was significant with p-value 0.044 (Table 3).

When similar changes were observed for proteinuria between baseline and follow-up times there was no significant shift noticed at 4th, 8th and 12th week with p-values 0.406, 0.306 and 0.416 respectively. At the end of study 3 of the 12 those who had proteinuria at baseline recovered completely and 1 of 38 that had no proteinuria developed proteinuria. (table.4 OR Figure.1)

Table 1: Basic characteristics of renal transplant patients

		Count	%
Cause of ESRD	Chronic GN	17	34.0
	b/l shruken kidney	11	22.0
	Diabetes	8	16.0
	Nephrolithiasis	6	12.0
	CIN	3	6.0
	Postpartum AKI	2	4.0
	vu reflex	2	4.0
	polycystic kidney	1	2.0
Previous HCV Tx Pre transplant	IFN 7 year back	1	2.0
	IFN 10 year back	1	2.0
	No	48	96.0
HLA match (x/6)	1.00	5	10.0
	2.00	7	14.0
	3.00	21	42.0
	4.00	9	18.0
	5.00	1	2.0
	6.00	7	14.0
Induction	ATG	8	16.0
	Basiliximab	4	8.0
	No	38	76.0
Immunosuppressive regimens(Y/mmf/delt)	Cyclo	4	8.0
	Tac	46	92.0
HCV genotype	3a	16	32.0
	3	13	26.0
	1a	9	18.0
	1	5	10.0
	2	4	8.0
	1 and 2	2	4.0
	1 and 3	1	2.0
Fibroscan	F0	4	8.0
	F1	26	52.0
	F2	15	30.0
	F3	5	10.0
NODAT	Yes	4	8.0
	No	46	92.0
proteinuria (mg/g creatinine) Baseline	Nil	38	76.0
	≤ 0.4	7	14.0
	0.41 – 0.6	4	8.0
	> 0.6	1	2.0

Table 2: Average values of biomarkers at four follow-up times and Comparison between times

Bio-markers	Baseline		Week 4		Week 8		Week 12		Friedman p-value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Bilirubin total mg/dl	0.8	0.2	0.8	0.2	0.8	0.2	0.8	0.2	0.446
ALT U/L	38.6	16.5	29.5	7.2	29.3	8.1	29.1	7.6	0.023
AST U/L	34.4	12.1	31.8	9.7	31.8	8.2	31.4	7.8	0.018
ALP U/L	147.3	44.8	122.6	36.6	114.3	36.2	107.4	34.9	<0.001
s/albumin g/dl	3.2	0.4	3.3	0.3	3.4	0.3	3.4	0.3	0.002
Hemoglobin g/dl	11.7	2.3	11.6	2.4	11.6	2.4	11.6	2.5	0.659
WBC count	10.6	3.1	9.3	2.9	9.3	2.8	9.1	2.9	0.005
Platelet count	228.0	51.3	230.1	66.5	239.0	78.1	243.2	81.9	0.816
s/creatine mg/dl	1.0	0.2	1.0	0.3	1.0	0.3	1.0	0.3	0.565
e GFR ml/min per 1.73 m	95.3	22.5	93.2	27.0	91.8	24.7	90.5	27.0	0.466
BSL mg/dl	102.2	30.8	97.1	21.8	93.0	14.8	89.6	10.7	0.008

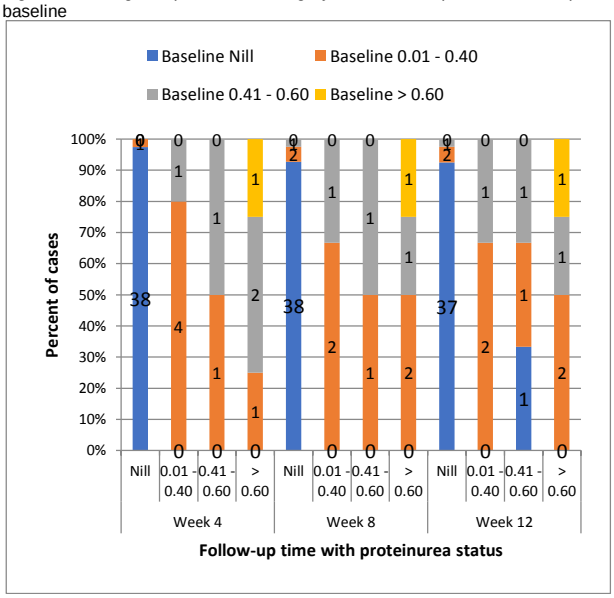
Table 3: Change in renal function category over follow-up times as compared to baseline

Time		Baseline							
eGFR (ml/min per 1.73 m)		> 90		60 – 90		30 – 60		Total	
		Count	%	Count	%	Count	%	Count	%
Week – 4	> 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 – 8	> 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 = 8.08		P-value = 0.044							

Table 4: Change in proteinuria category over follow-up times as compared to baseline

Time		Baseline									
Proteinuria (mg/g creatinine)		Nill		0.01 - 0.40		0.41 - 0.60		> 0.60		Total	
		Count	%	Count	%	Count	%	Count	%	Count	%
Week 4	Nill	38	100.0	1	14.3	0	0.0	0	0.0	39	78.0
	0.01 - 0.40	0	0.0	4	57.1	1	25.0	0	0.0	5	10.0
	0.41 - 0.60	0	0.0	1	14.3	1	25.0	0	0.0	2	4.0
	> 0.60	0	0.0	1	14.3	2	50.0	1	100.0	4	8.0
	Total	38	100.0	7	100.0	4	100.0	1	100.0	50	100.0
McNemar = 4.00						P-value = 0.406					
Week 8	Nill	38	100.0	2	28.6	1	25.0	0	0.0	41	82.0
	0.01 - 0.40	0	0.0	2	28.6	1	25.0	0	0.0	3	6.0
	0.41 - 0.60	0	0.0	1	14.3	1	25.0	0	0.0	2	4.0
	> 0.60	0	0.0	2	28.6	1	25.0	1	100.0	4	8.0
	Total	38	100.0	7	100.0	4	100.0	1	100.0	50	100.0
McNemar = 6.00						P-value = 0.306					
Week 12	Nill	37	97.4	2	28.6	1	25.0	0	0.0	40	80.0
	0.01 - 0.40	0	0.0	2	28.6	1	25.0	0	0.0	3	6.0
	0.41 - 0.60	1	2.6	1	14.3	1	25.0	0	0.0	3	6.0
	> 0.60	0	0.0	2	28.6	1	25.0	1	100.0	4	8.0
	Total	38	100.0	7	100.0	4	100.0	1	100.0	50	100.0
McNemar = 5.00								P-value = 0.416			

Figure 1: Change in proteinuria category over follow-up times as compared to baseline



DISCUSSION

HCV-positive renal transplant patients are associated with increased risk of chronic allograft rejection, transplant glomerulopathy, HCV associated glomerulonephritis, and post-transplant diabetes resulting in early graft loss. These patients have decreased long-term post-transplant survival and also are on increased risk of mortality and morbidity due to cardiovascular complications, infections and liver disease, as compared to Non-HCV positive renal transplant population[20,21,22].

The negative effects of HCV on renal transplant outcomes were demonstrated in a recent meta-analysis including 133,350 transplant recipients. They observed as compared to HCV-negative recipients, HCV positive patients had a 76% and 85% increased risk of graft loss and increased risk of all-cause mortality respectively[22].

In our study, SVR after 12 weeks of treatment with DAA in our study population was 100% which was comparable to previous studies. Lubetzky et al[23] in his study observed 100% SVR after 12 weeks of treatment which is similar to our finding. Beinhardt et al[24] also observed 96% SVR after 12 weeks of treatment with DAA. Colombo et al[28] study including 114 kidney transplant recipients with HCV infection and with a filtration rate (eGFR) of 40mL/min or greater, all of his study population achieved SVR after 12 weeks of treatment.

Liver function was significantly improved after DAA therapy. The alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were reduced significantly after initiation of Treatment. Kamar et al[25] in his study as well as Sawinski et al[26] also observed similar finding.

We observed that allograft function (eGFR and serum creatine) was not significantly different in pre and post DAA therapy, moreover we also found no acute rejection episode or graft loss was observed with DAA therapy and similar finding was also observed by Lubetzky et al[23]

No significant change in proteinuria was observed during treatment. Eisenberger et al [27] observed similar finding.Our study has some limitations. This was a single centre experience with a relatively small sample size.

CONCLUSION

HCV is a well-recognised risk factor of poor graft survival in kidney transplant patients. In our study, it was observed that DAA treatment can resolve HCV infection in kidney Transplant Recipients with significant improvement of liver function without loss of allograft function.

Acknowledgement: We would like to thank Muhammed Asim for statistical review and doctors along with supporting staff in Nephrology department of Bahria International Hospital, Lahore for continuing encouragement.

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

Disclaimer: None to declare

Funding Disclosure: None to declare

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