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SAFETY AND EFFICACY OF DIRECTLY ACTING ANTIVIRAL AGENTS IN CHRONIC HEPATITIS C INFECTED HEMODIALYSIS DEPENDENT PATIENTS: A SINGLE CENTER CROSS-SECTIONAL STUDY

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Abstract:
Chronic Hepatitis C virus infection is a matter of universal health concern, more so in a third world country like Pakistan with significant disease prevalence. Patients with end stage renal disease (ESRD) who are on maintenance hemodialysis are at an increased risk for developing this infection due to various factors. The introduction of direct acting anti-viral (DAA) therapy for hepatitis C has simplified treatment. However, challenges related to drug clearance and ribavirin induced anemia persist in patients with ESRD. The aim of this study was to assess the efficacy and safety of DAA therapy in chronic HCV patients requiring maintenance hemodialysis. 73 patients were analyzed, who received a 12-week course of sofosbuvir and velpatasvir (without ribavirin). Sustained virological response at week 12 (SVR-12) was achieved in 97.3% of the patients, equivalent to cure. No treatment related side effects were noted in 40% of the patients, while remaining patients experienced mild adverse effects not requiring treatment interruption or withdrawal. Hence, our study proved that DAA therapy was both effective and safe in our patients with ESRD and simultaneous chronic HCV infection.

Key words: Chronic HCV infection, end stage renal disease, hemodialysis, direct acting anti-viral therapy.

Introduction:

Hepatitis C virus (HCV) infection contributes to a significant burden of chronic liver diseases on a global scale, with approximately 3% of the world's population being affected by the disease[1]. In Pakistan, the prevalence is even higher, with 4.3% of individuals suffering from chronic HCV infection[2]. The introduction of directly acting antiviral (DAA) therapy few years ago has revolutionized the management of HCV. Apart from treatment naïve individuals, DAAs have also shown favorable therapeutic response in those patients who have failed previous treatment, or who have decompensated chronic liver disease[3].

Occurrence of HCV infection in patients with end-stage renal disease (ESRD) is evidently greater than what is seen in the population in general[4]. In Pakistan, for example, prevalence of HCV positivity in such patients has been reported to be close to 10%[5]. These patients can acquire the infection from improperly screened blood transfusions, and nosocomial infection due to contaminated hemodialysis equipment or use of multidose drug vials. For this reason, Center of Disease Control (CDC) recommends routine screening for HCV in these high risk individuals. Furthermore, HCV infection in patients with ESRD carries a poor overall prognosis, not only due to immune-mediated glomerular injury causing further renal damage, but also because these patients rapidly progress to chronic liver disease, also leading to high mortality rate as a result of various liver related complications[6]. Additionally, this subset of patient population was previously considered to be "difficult to treat" due to the various drug side effects (when interferon therapy was the back-bone of HCV management) and hence many of the patients with advance kidney disease and HCV infection remained untreated or partially treated[7].

The use of DAA in patients on maintenance hemodialysis hypothetically has its own problems, especially drug clearance through hemodialysis and the occurance of ribavirin induced anemia[8]. Nevertheless, there is a growing trend of utilizing DAA therapy to treat such patients with coexisting ESRD with promising treatment outcomes[9]. Most treatment guidelines have endorsed DAA therapy as standard of care for the treatment of HCV infection in patients requiring maintenance hemodialysis[10].

With abundant data exist regarding the efficacy and safety of DAAs internationally, there is nevertheless a scarcity of local literature relevant to this essential aspect of the management of HCV. This especially holds true in a country like Pakistan where a high number of hemodialysis patients are at increased risk of acquiring HCV infection due to unsafe medical practices. Therefore, the objective of our study was to analyze the safety and efficacy of direct acting antivirals in patients with chronic hepatitis C requiring hemodialysis.

Methods:

This was a retrospective chart review. All ESRD patients attending the out-patients department of the Ziauddin Hospital, Karachi, aged 18 years or above (either with compensated or decompensated chronic liver disease) with chronic hepatitis C, who had received therapy with direct acting antivirals, were included in this study. Active alcohol users, those with metastatic malignancy, and those with HBV and/ or HIV co-infection were excluded.

Demographic data of the patients were obtained through a pre-designed questionnaire. Demographic data regarding age, gender and co-morbid illnesses were collected. Laboratory data including complete blood count, liver function tests, creatinine, HCV PCR detection (pretreatment and 12 weeks post-treatment i.e. sustained virological response at week 12 {SVR-12}), HCV genotype, and transient elastography were also collected. Efficacy and safety of the therapy was assessed by analyzing the SVR rates and the side effects of the drugs respectively.

Data analysis procedure:
Data was analyzed using SPSS version 21. A descriptive analysis was done for demographic, and laboratory features. Mean ± standard deviation was calculated for quantitative variables. Frequencies and proportions were reported for qualitative variables. Moreover, frequency and percentages of outcome variable was also calculated.

Results:
In total, 73 patients with ESRD requiring hemodialysis who had received DAA therapy to treat chronic HCV infection at our hospital were included in the study. All patients received a combination of sofosbuvir and velpatasvir for 12 weeks. None of the patients included in this study received ribavirin along with DAA. The median age of the patients included in this study was 52 years with an IQR of 18 years. 56.2% (n=41) of the patients were male while 43.8 % (n=32) were female. 94.5% of the study participants were naïve patients with no prior exposure to anti HCV therapy. Hypertension was the most common co-morbid illness with a proportion of 32.9% (n=24), followed by type II Diabetes Mellitus with a proportion of 13.7% (n=10). 60% of the patients were infected by Genotype-3 of Hepatitis C virus. Among all the patients, 78.1% were diagnosed with compensated chronic liver disease (either normal liver parenchyma or features liver cirrhosis without ascites), while 21.9% (n=16) had decompensated chronic liver disease (with ascites) when assessed with the help of abdominal ultrasound. The data of transient elastography revealed that 56.2% (n=41) of all the patients included in this study were found to have little or no scarring or fibrosis of liver parenchyma (Table: 1).

Sustained virological response at 12 weeks after completion of anti-HCV therapy (SVR-12) was calculated to determine the efficacy of DAA therapy. 97.3% (n=71) of patients achieved SVR-12, while only 2.7% (n=2) patients didn't show response to the DAA therapy.

The study compared the demographic and health related characteristics as well as biochemical parameters of haemodialysis patients who responded to the DAA therapy as assessed in terms of SVR-12 with those who didn't respond to DAA therapy. This study found no statistically significant differences in the characteristics of the two groups with different SVR-12 (Table: 2).

Almost 40% (n=29) of all the patients on haemodialysis who received DAA therapy for chronic HCV infection didn't report any side-effect in response to treatment. However, altogether 43.8% (n=32) of the study participants either experienced headache or body ache or both during therapy. Headache alone was the most common side effect as reported by 21.9% (n=16) of the study participants, followed by body aches as reported by 15.1% (n=11). 9.6% (n=7) reported a flu-like illness. Diarrhea was experienced by 4.1% of the patients while fever and arthritis were among the least reported side-effects by haemodialysis patients who received DAA therapy (Figure: 1).

Discussion:
For years, treatment of chronic HCV infection in patients who require maintenance hemodialysis has been a challenge. The various side effects of interferon therapy which included extreme fatigue, flu-like symptoms and psychiatric disturbances and the tedious subcutaneous route of administration further added to the misery of this subset of patient population, ending up in treatment discontinuation for many of them. However, the advent of DAA therapy has significantly augmented the chances of cure for these patients, especially as these oral drugs are more efficacious and relatively well-tolerated as opposed to the ones previously being used[11]. Therefore, we aimed to evaluated the efficacy (in terms of achieving SVR-12) and tolerability of DAA therapy in our setup where hepatitis C infection is a major health problem, and a lot of patients on maintenance hemodialysis unknowingly acquire this infection either nosocomially or due to faulty health practices.

Sofosbuvir, a nucleotide polymerase inhibitor, has been the cornerstone of DAA therapy for chronic HCV infection for nearly a decade now. It is the only drug amongst the DAAs which is mainly eliminated by the kidneys. Therefore, international guidelines propose that sofosbuvir should be used guardedly in patients with severe renal insufficiency and ESRD, without any dose recommendation[10]. Interestingly, however, studies with large sample size have incorporated sofosbuvir-based treatment regime in treating ESRD patients and chronic HCV infection with promising results[12].

All patients in our study were treated with sofosbuvir and velpatasvir (NS5A replication complex inhibitor) for a period of 12 weeks, which is currently the "standard of care" for treating chronic HCV patients in Pakistan. Notably, ribavirin was not part of the treatment regimen for any of the patients due to the potential risk of aggravating anemia. This is in congruence with other studies from Pakistan which have utilized similar treatment schedule[13, 14]. There is some data regarding the favorable treatment outcomes of sofosbuvir and daclatasvir (NS5A inhibitor) in such patients as well[15]. However, the sample size in most of these studies was small, hence the need of a bigger study with larger sample size has always been the need of the hour.

In similarity to previous studies, our study also showed impressive SVR-12 rates with the combination of sofosbuvir and velpatasvir. This response was even better than what had been achieved with sofosbuvir and daclatasvir for treating patients with chronic HCV infection and on maintenance hemodialysis[15,16]. The cure rates reported in our study are comparable to what is commonly observed in chronic HCV patients with normal renal functions[17]. We also found no difference in the demographic, biochemical parameters and health related characteristics among the responders and non-responders to DAA therapy. However, it is difficult to say whether these factors really affect treatment outcomes in this subset of patients as the number of non-responders is fairly low and the groups are not equivalent in terms of patient numbers.

Finally, an encouraging finding in our study was the fact that almost half of the patients receiving DAA therapy for chronic HCV infection did not experience any drug related side effects throughout the treatment duration and beyond (i.e. upto 12 weeks after treatment completion). Additionally, the side effects reported by the rest of the patients were of not of severe nature, as none of the adverse effects led to cessation of therapy. Hence, we confirmed the findings of earlier studies which clearly showed that sofosbuvir-based treatment regimens are well tolerated in patients with ESRD[18].

The major strength of this study is that it presents a large data of patients with ESRD from Pakistan, who have been treated with the newer DAA therapy, especially sofosbuvir and velpatasvir for chronic HCV infection. However, being a single center study, the results cannot be extrapolated to the population at large. Furthermore, the retrospective cross-sectional design somewhat makes the level of evidence less robust as compared to prospective studies and is prone to recall bias.

Conclusion:

Our manuscript presents valuable understanding into the efficacy as well as tolerability of DAA therapy in patients on maintenance hemodialysis and concomitant chronic active HCV infection. We believe that the high SVR-12 rates (>95%) and the favorable side effect profile of these medications when used in ESRD patients will be a source of encouragement for physicians who are involved in the management of such patient population. However, additional prospective studies are required to further consolidate these findings, especially the effect of demographics and other patient related characteristics in terms of responders and non-responders to DAA therapy.

Conflict of interest: None.
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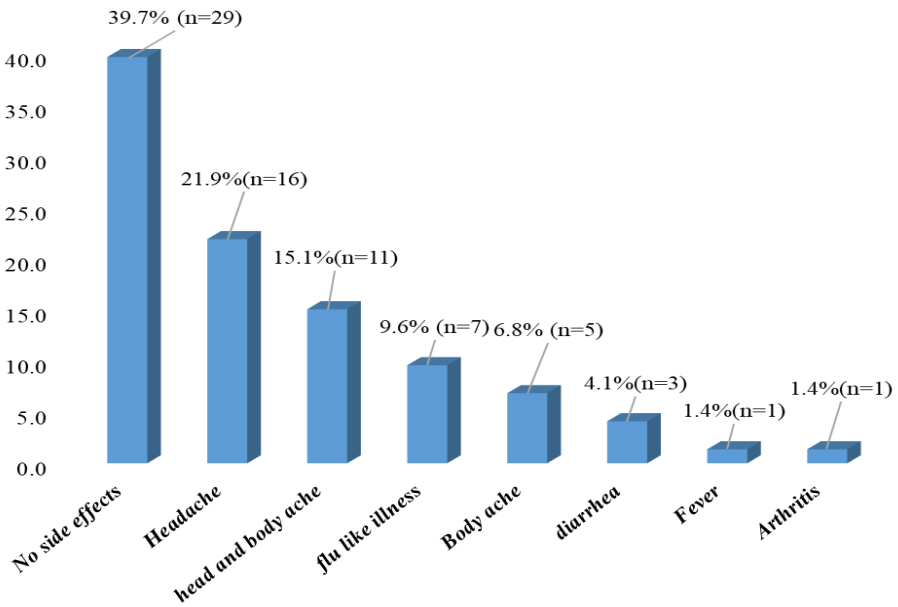
Table:1 Demographic and Disease related Characteristics of chronic HCV patients treated with DAA Therapy (n=73)		
Variable	**Frequency**	**Percentage**
Age (in completed years)		
Median age 52years (IQR = 18 years)		
18-36 years of age	22	22.0
37-54years	37	37.0
55years and above	41	41.0
Sex		
Male	41	56.2
Female	32	43.8
Patient type		
Treatment naïve	69	94.5
Treatment experienced	04	5.5
Co-morbid illness		
Hypertension	24	32.9
Diabetes Mellitus	10	13.7 6.8
Ischemic Heart Disease	05	11
Others	08	
HCV Genotype (n=63)		
Type-1	09	14.3
Type-2	15	23.8
Type-3	38	60.3
Type-4	01	1.6
Diagnosis on abdominal sonography		
Decompensated chronic liver disease	16	21.9
Compensated chronic liver disease	57	78.1
Grading on transient elastography		
F0-F1-Little or no scaring	41	56.2
F2 -Mild Scaring	16	21.9
F3- Moderate Scaring	12	16.4
F4-Severe Scaring / Cirrhosis	04	5.5
Sustained virological response at week 12		
PCR Negative	71	97.3
PCR Positive	02	2.7
Multiple responses possible**		

Table:2 Comparison of various clinical and biochemical parameters among chronic HCV patients with and without successful SVR-12 after DAA Therapy (n=73)			
	End Treatment Response		
Variables	**PCR Positive (n=2)**	**PCR Negative (n=71)**	**p-value**
Age (in completed years)			
18-36 years of age	0	07(10)	
37-54years	1(50)	40(57.1)	1.0
55years and above	1(50)	23(32.9)	
Sex			
Male	01(50)	31(43.7	1
Female	01(50)	40(56.3)	
HCV Genotype (n=63)			
Type-1	0	09(14.8)	
Type-2	0	15(24.6)	1.0
Type-3	2(100)	36(59.0)	
Type-4	0	01(1.6)	
Diagnosis on abdominal sonography			
Decompensated chronic liver disease	0	16	1.0
Compensated chronic liver disease	02	55	
Grading on transient elastrography			
F0-F1-Little or no scaring	0	41(57.7)	

F2 -Mild Scaring F3- Moderate Scaring F4-Severe Scaring / Cirrhosis	01(50) 01(50) 0	15(21.1) 11(15.5) 04(5.6)	0.20
Serum Albumin Levels Median (IQR)	2.4 (0)	3.7(1)	1.0
Serum SGPT Median (IQR)	58(48)	48(56)	0.48
Serum INR Median (IQR)	1(1)	01(1)	0.51
Serum Haemoglobin Median (IQR)	11.2(11.1)	10.2(1.6)	0.41
Platelet Count Median (IQR)	100.5(0)	159(73)	0.47
Serum TSH Median (IQR)	9.4(3.2)	2.6(2.3)	0.34
Serum Urea Median (IQR)	116(0)	90(19)	0.86
Serum Creatinine Median (IQR)	6.5 (6.3)	8(3.25)	0.47
Duration on Haemodialysis (in years)	4(3)	3(2.5)	0.77

Figure 1: Frequency Distribution of various side-effects of DAA Therapy for Hepatitis-C infection as experienced by Haemodialysis Patients in a Private Tertiary Care Hospital In Karachi (n=73)*



Multiple responses possible*

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