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Chronic HCV in CKD-Experience with Oral Antiviral at Tertiary Care Centre of Northern India

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[&]Author Contribution:

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1. Abstract

1.1. Introduction: Chronic hepatitis C is one of the most common cause all over the world for causing cirrhosis of liver. It is commonly seen in Chronic Kidney Disease (CKD) patients who are on maintenance dialysis and treatment with oral directly acting antiviral is challenging due to renal side effects of sofosbuvir which is integral part of treatment regimen.

1.2. Conclusion: The Sofosbuvir containing oral antiviral regimens are safe in CKD even when used in full dosages and have lesser side effects, good compliance and excellent sustained virological response.

2. Introduction

Hepatitis C Virus (HCV) infection has effected over 71 million people worldwide [1] andproportion of cirrhosis in chronically infected patients is rising and projected to reach 44.9% by 2030 [2]**.** Persons infected with hepatitis C virus (HCV) can develop kidney disease as a result of extra hepatic manifestation of HCV or as a disease process independent of the HCV infection. In addition, hemodialysis has been a risk factor for acquiring HCV infection, as shown by numerous outbreaks and HCV cross-infections that have occurred in hemodialysis units [3-6]**.** Earlier studies conducted in western countries have shown an HCV prevalence in hemodialysis patients that ranged from 2.6 to 23%, with higher prevalence correlating with longer duration of hemodialysis [7-9].The risk of HCV transmission in hemodialysis units has declined due to improved testing and infection control practices [10,11].Several studies have shown that patients on chronic hemodialysis have an increased overall mortality risk if they have chronic hepatitis C infection when compared with those on dialysis who do not have hepatitis C infection [12-14]. There are also some data showing that chronic hepatitis C may be a risk factor for developing renal cell carcinoma [14]. Chronic hepatitis C infection has also been associated with an accelerated course of renal disease, including in persons with HIV coinfection [15,16]. Extra hepatic manifestations related to HCV, including immune complex-related renal disease, can require urgent HCV treatment to resolve or prevent further organ damage (Figure 1). The wide availability of multiple pan-genotypic, oral, Direct-Acting Antiviral (DAA) drugs has completely changed the scenario of HCV treatment. These DAA regimens are simple, safe, to be taken orally once a day, well-tolerated, highly effective with reported Sustained Virologic Response (SVR) rates exceeding 95% in patients with compensated liver disease [17]. The SVR leads to improvement in HCV-related liver damage, leading to liver fibrosis regression and a reduction in the incidence of Hepato Cellular Carcinoma (HCC), thereby prolonging overall survival [18-21]. The availability of Direct-Acting Antiviral Agents (DAAs) has sparked major enthusiasm for treating persons with HCV who have chronic renal impairment, especially since many of these individuals historically have not been eligible for treatment given the toxicities associated with interferon and ribavirin-based therapies [22]**.**

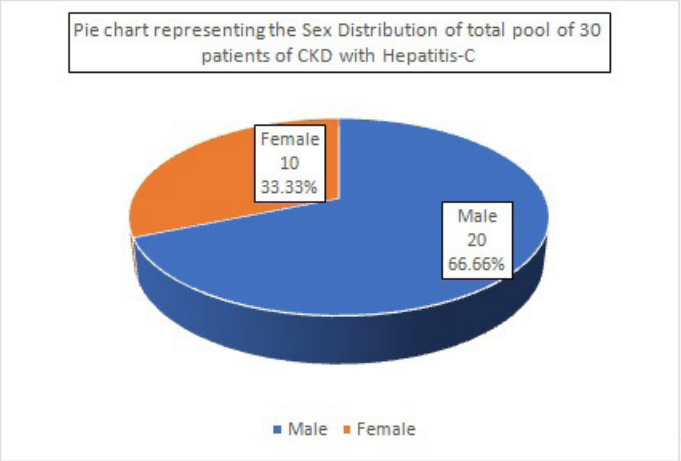

Figure 1: Showing Sex Distribution of Total Chronic Hepatitis C Patients

3. Aim

To determine the Sustained Virological response in Chronic Kidney disease patients treated with full dose of directly acting oral antiviral drugs i.e. Sofosbuvir 400 mg & Daclastavir 60 mg, Sofosbuvir & Velpatasvir 100 mg and Sofosbuvir 400 mg & Ledipasavir 90 mg).

4. Material and Methods

It was prospective study conducted at Department of Medical Gastroenterology, Post Graduate Institute of Medical Sciences (PGIMS), Rohtak, over a period of five years from 01.01.2016 to 31.12.2020. Out of four thousand patients of chronic hepatitis C who reported in department in above five years duration, 44 patients were having Chronic Kidney disease with stage 5. Out of these 44 patients, pre therapy HCV RNA was not detected in 3 patients, hence they were not treated and were not part of the study (Table 1). The remaining 41 patients, who were treatment naive, were put on full dose of antiviral treatment as per scientific indication, after proper consent and explaining clearly about unexpected renal side effects of Sofosbuvir and need of regular follow up with their Nephrologists. Out of these 41 patients, 3 left treatment in between and died, 8 patients completed treatment but died due to baseline CKD before SVR testing could have been done in them. Hence these 11 patients were excluded from the study and data pertaining to 30 patients was analyzed.

Table 1: Showing Distribution Among Total Pool of Chronic HCV with CKD Patients

Total Number of CKD with HCV Patients	Males	Females	Rural Background	Urban Background	Cirrhotic	Non Cirrhotic
30	20 (66.66%)	10 (33.33%)	19 (63.33%)	11 (33.66%)	5 (16.66%)	25

4.1. Stastical Analysis

All the data was entered in Microsoft Excel and was analysed using SPSS 15.0 version.

5. Observation & Results

Out of four thousand patients of Chronic hepatitis C who reported in department in above five years duration, ultimately data pertaining to thirty confirmed patients of CKD with HCV who remained on regular follow up was analyzed. Out of these 30 patients, 20 (66.66%) were males and rest ten were females (33.33%). On analyzing age distribution of these 30 patients, highest numbers of patients were seen in 30 yrs-50 yrs of age group (17 patients i.e. 56.66%). Majority of patients belonged to poor socio economic status and had rural background i.e. 19 patients (63.33%) and 11 patients (36.66%) belonged to urban areas. Out of 30 patients, only five patients were cirrhotic (16.66%), rest all was non-cirrhotic (Table 2). The younger age group of patients, non-cirrhotic group predominance and lesser side effects led to good compliance rate i.e. 38 patients out of 41 completed their treatment i.e. 92.68%. The HCV viral load varied from 10^2 - 10^7 I.U. with mean of 10^6 I.U., thereby implying that majority of patients had high viral load. Out of these 30 patients, 18 patients (60 %) were treated with Sofosbuvir & Daclastavir combination, 7 patients (23.33%) with Sofosbuvir & Ledipasavir combination and 5 patients (16.66 %) were treated with Sofosbuvir & Velpatasvir combination. Out of 30 CKD patients who were treated with above oral antiviral, 29 patients (96.66%) achieved Sustained Virological Response (SVR) (Table 3). Only two patients in above pool of CKD patients got renal transplantation till date. Out of them one patient expired after renal transplant and other one is living normal life on immunoprophylaxis.

Table 2: Showing Age Distribution in Chronic HCV with CKD Patients

CKD with HCV Patients	10-20 yrs	20-30 yrs	30-40 yrs	40-50 yrs	50-60 yrs	60-70 yrs
30	1 (3.33%)	5 (16.66%)	10(33.33%)	7 (23.33%)	3 (10%)	4 (13.33%)

Table 3: Showing Oral Antiviral Distribution in Chronic HCV with CKD Patients

CKD with HCV Patients	Sofosbuvir & Ledipasavir	Sofosbuvir & Daclastavir	Sofosbuvir & Velpatasvir	HCV RNA Load
30	7 (23.33%)	18 (60 %)	5 (16.66%)	10^2 - 10^7 I.U. (mean of 10^6)

6. Discussion

All the 30 CKD patients in our study group were in CKD stage 5 on regular hemodialysis. There was male predominance which correlates with major representation of males in overall group of four thousand HCV patients from which these 30 CKD patients were treated. Hence, it cannot be inferred that HCV in CKD is more common in male gender. Similarly, the majority of patients belonged to poor socioeconomic status with rural background which also correlates with their dominance in overall group of HCV patients. The maximum representation of younger age group from 20-50 yrs of age group also matches with their proportion in overall group of four thousand patients of Chronic HCV. The side effects were observed in only three patients that too mild in form of anemia and generalized weakness which can also be attributed to baseline Chronic kidney disease. Out of 30 patients, only five patients were cirrhotic (16.66%), rest all was non-cirrhotic. The younger age group of patients, non-cirrhotic group predominance and lesser side effects led to good compliance rate i.e. 38 patients out of 41 completed their treatment i.e. 92.68%. The HCV viral load varied from 10^2 - 10^7 I.U. with mean of 10^6 I.U., thereby implying that majority of patients had high viral load. The patients were treated with oral antiviral and ribavarin was not used at all. As this is five year study, so initially as per government guidelines, genotype based treatment was given i.e. genotype 1 & 4 were treated with Sofosbuvir & Ledipasavir and genotype 3 was treated with Sofosbuvir & Daclastavir. Later on guidelines were changed under National Viral Hepatitis Program (NVHCP) and genotype testing was stopped and non-cirrhotic were treated with Sofosbuvir & Daclastavir and cirrhotic with Sofosbuvir & Velpatasvir. Out of 30 CKD patients who were treated with above oral antiviral, 29 patients (96.66%) achieved Sustained Virological Response (SVR). It is in line with observational cohort study conducted in the Veterans Administration system, in which investigators used the Electronically Retrieved Cohort of HCV Infected Persons (ERCHIVES) to analyze HCV treatment responses for 13,663 persons who received ledipasvir-sofosbuvir, with or without ribavirin. This cohort included a total of 1,607 with CKD stage 3, 4, or 5 who completed HCV treatment. The SVR12 rates for individuals with stage 3 CKD who completed treatment was 97.0% (1080 of 1113) in those who received ledipasvir-sofosbuvir and 97.1% (375 of 386) with ledipasvir-sofosbuvir plus ribavirin [23]**.** For those with stage 4 or 5 CKD, the SVR12 rates were 94.0% (78 of 83) with ledipasvir-sofosbuvir and 100% (25 of 25) with ledipasvir sofosbuvir plus ribavirin. In another phase 2, single-arm study, 59 adults with HCV genotype 1, 2, 3, 4, 5, or 6 and ESRD undergoing hemodialysis or peritoneal dialysis received open-label sofosbuvir-Velpatasvir (400 mg/100 mg) once daily for 12 weeks [24]. The participants included treatment-naïve or experienced individuals, with and without compensated cirrhosis. Overall, 95% (56 of 59) of the participants achieved an SVR12. Serious adverse events occurred in 11 persons, but the adverse effects were thought to be unrelated to the HCV treatment medications [24]. The AASLD-IDSA HCV Guidance now recommends that no dose adjustment is required for HCV treatment in persons with renal impairment when the treatment regimen is a recommended regimen [25]. The one exception is that if ribavirin is added to a regimen, dose adjustment of the ribavirin is required, as noted in the prior section [2]. We also followed the same guidelines and all patients were treated with full dosages of oral antiviral, even with sofosbuvir.

7. Conclusion

During the initial period of oral antiviral, there was hitch in treatment of CKD patients especially with Sofosbuvir containing regimens but now many studies have reported high compliance rates and SVR and good tolerability with Sofosbuvir based therapy, that too in full dosages in background of majority of patients having high viral load. The ideal treatment for this group of CKD with HCV is to make them virus free and get them kidney transplant as early as possible. In India due to limitation of donors and financial restrictions, very limited number of patients gets ultimately transplanted but making such patients HCV free can decrease overall morbidity and mortality & can buy more time before they make it to transplant.

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