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Outcome of Direct Acting Antiviral Drugs (DAADs) for Hepatitis C Virus (HCV) in the Setting of Chronic Kidney Disease (CKD) in Upper Egypt

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ABSTRACT

Background: The frequency of hepatitis C virus (HCV) infection remains high in patients with CKD and plays a detrimental role in mortality in this population, and patients undergoing maintenance dialysis are still at risk of developing HCV infection and HCV disease prevalence of anti-hepatitis C virus (HCV) patients who undergo long-term dialysis are significantly greater than those with normal kidney function. **Objectives**: The aim of the study was to assess outcomes (efficacy, side effects, and possible complications) of DAADs for HCV in presence of CKD. **Subjects and methods:** this was retrospective cohort study that was conducted at Aswan Fever Hospital and Luxor Fever Hospital for anti HCV therapy between Jan 2018 and July 2018 including 60 patients recruited from both hospitals with all stages of CKD and were receiving DAADs. **Results**: the results revealed that PC (%) in patients from Aswan ranged between 61-100 with mean ±S.D. 83.09±9.258 while in patients from Luxor it ranged between 66-100 with mean ±S.D. 84.95±6.764. There was no statistically significant difference between groups (P=0.458). HCV PCR in all patients from Aswan at baseline were positive while after 3 months 27 (90%) were negative and 3 (10%) were positive and after 6 months all patients were negative while in patients from Luxor they all were positive while after 3 months 28 (93.3%) were negative and 2 (6.7%) were positive and after 6 months all patients were negative. There was no statistically significant difference between groups.

Conclusion: Treatment with newer DAAs is effective and safe for the treatment of HCV-infected chronic kidney disease patients.

Keywords: DAAs, Kidney, Treatment, CKD, HCV.

INTRODUCTION

Globally, an estimated 170-180 million people are infected with the hepatitis C virus (HCV), resulting in 500,000 deaths annually [(1)]. Egypt has the highest prevalence of hepatitis C virus worldwide, with a prevalence rate (14.7%). If left untreated, CHC can progress to cause fibrosis, cirrhosis, liver compensation, or hepatocellular carcinoma (HCC) [(2)]. Additionally, there are several extrahepatic manifestations of CHC, including kidney disease [(3)].

Kidney disease is common with chronic hepatitis C virus (HCV) infection. Kidney diseases associated with hepatitis C virus are mainly complex immune disorders such as mixed blood globulin and MPGN [(4)]. In patients with end-stage kidney disease (ESRD), there is also a higher prevalence of viral hepatitis infection due to the increased risk of transmission associated with dialysis [(5)].

Hepatitis C infection has significant risks of morbidity and mortality in this population and thus, creates a mandate for screening and treatment of hepatitis C in patients with CKD [(6)]. In the era of direct-acting antiviral drugs (DAADs), HCV infection can be successfully treated in patients with advanced kidney disease. The development of systems based on DAADs that are not renally filtered has created new options for treating hepatitis C in advanced kidney disease, as protease inhibitors and non-structural protein 5A (NS5A) inhibitors are cleared by the liver with minimal renal excretion, and thus they are currently the most common option. It is a safe treatment for patients with ESRD with genotype 4 infection [(7)].

In addition, patients with advanced renal disease and severe hepatic impairment (Child-Pugh-Turcotte Class B or C) are largely left untreated, as the benefits of treating these patients with multiple organ failure remain uncertain. At this time, the DAAD regimens used in renal impairment are not in patients with severe hepatic impairment resulting from recommended hepatotoxicity, impaired hepatic clearance of drugs, and lack of data in decompensated cirrhosis [(8)].

The aim of the study was to assess outcomes (efficacy, side effects, and possible complications) of DAADs for HCV in presence of CKD.

SUBJECTS AND METHODS

This study is retrospective cohort study, which was conducted at Aswan Fever Hospital and Luxor Fever Hospital for anti HCV therapy between Jan 2018 and July 2018. About 60 patients with all stages of CKD who were receiving DAADs were recruited from both hospitals.

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Inclusion Criteria: 1.Patients with CKD with HCV RNA positive PCR. 2. Receiving DAADs.

Exclusion Criteria: 1.Patients on dialysis, 2.Patients with Hepatocellular carcinoma (HCC), 3.Patients with combined HCV and HBV infection and 4.Patients with decompensated liver cirrhosis.

Study groups: Group A included patients in Aswan Fever Hospital. Group B included patients in Luxor Fever Hospital.

Methodology:

Ethical approval:

After taking informed written consent from National Committee for Control of Viral Hepatitis (Ministry of Health).

We were gathering information to study the efficacy of treatment in the form of: sustained viral response (SVR) and/or relapse after treatment for 3 months and 6 months. Patients in need to repeat, modify, or change protocol of treatment.

Also monitoring any progress in kidney functions weather deterioration or improvement. Assessment of any renal complications could happen as cryoglobulinemia, proteinuria, and/or deterioration in kidney functions. Assessment of liver functions, coagulation profile, anemia, rash, etc.

- **History taking:** age, sex, location, risk factors, causes of CKD, family history, detecting also inclusion and exclusion criteria.
- **Examination:**
- ***General examination:*** Arterial blood pressure, pulse, temperature, anemia, jaundice, puffiness, swelling.
- ***Abdominal examination:*** Assessment of any masses, swelling, ascites, or tenderness.
- ***Lower limb examination:*** Assessment of lower limb edema or tenderness.
- **Investigations:** Urine analysis, urine protein/creatinine ratio. Renal function tests (urea, creatinine). PCR for HCV RNA to assess sustained viral response (SVR) after treatment for 3 months and 6 months. Liver function tests (AST, ALT, albumin, bilirubin, prothrombin, etc.). Abdominal ultrasound and full blood count.

Statistical Analysis

The collected data were revised, organized, tabulated and statistically analyzed using statistical package for the social sciences (SPSS) version 22.0 for windows. Data are presented as the range, mean ± standard deviation (SD), frequency, and percentage. Continuous normally distributed data were compared by the Student t test (two-tailed) and categorical data were compared using Chi^2 test. The level of significance was accepted if the P value < 0.05.

RESULTS

There was no statistically significant difference between groups as regard HCV PCR (Table 1).

Table (1): Comparison between two groups as regard to HCV PCR

HCV PCR	Aswan (n=30)		Luxor (n=30)		P Value
	No.	%	No.	%	
Baseline					
Negative	0	0	0	0	1
Positive	30	100	30	100	
After 3 months					
Negative	27	90	28	93.3	0.640
Positive	3	10	2	6.7	
After 6 months					
Negative	30	100	30	100	1
Positive	0	0	0	0	

As regard to ALT; there was no statistically significant differences between groups (Table 2).

Table (2): Comparison between two groups as regard to patient's ALT

ALT	Aswan (n=30)	Luxor (n=30)	P Value
Mean± S.D	32.57±4.342	32.73±6.037	0.980

The difference in AST between Aswan and Luxor was not statistically significant (Table 3).

Table (3): Comparison between two groups as regard to patient's AST

AST	Aswan (n=30)	Luxor (n=30)	P Value
Mean± S.D	38.40±2.426	34.33±2.736	0.488

There was no statistically significant differences between groups as regard Hb (Table 4).

Table (4): Comparison between two groups as regard to patient's Hb

Hb	Aswan (n=30)	Luxor (n=30)	P Value
Mean± S.D	12.247±1.821	12.78±1.655	0.240

There was no statistically significant differences between groups regarding creatine (Table 5).

Table (5): Comparison between two groups as regard to patient's creatine

Creatine	Aswan (n=30)	Luxor (n=30)	P Value
Mean± S.D	2.55±0.837	2.257±0.468	0.099

There was no statistically significant differences between groups as regard patient's PC (%) (Table 6)

Table (6): Comparison between two groups as regard to PC (%)

PC (%)	Aswan (n=30)	Luxor (n=30)	P Value
Mean± S.D	83.09±9.258	84.95±6.764	0.378

DISCUSSION

The present study shows that HCV PCR in patients from Aswan at baseline in all patients was positive while after 3 months 27 (90%) were negative and 3 (10%) were positive and after 6 months all patients were negative while in patients from Luxor all patients were positive while after 3 months 28 (93.3%) were negative and 2 (6.7%) were positive and after 6 months all patients were negative. There were no statistically significant differences between groups.

Muñoz-Gómez *et al.* [9] reported that most of them were infected by HCV genotype 1b (n=32; 69.6%).

Approximately more than 170 million patients have chronic hepatitis C virus (HCV) infection worldwide, leading to 500,000 deaths annually. Chronic HCV infection can progress to liver fibrosis, liver cirrhosis, and hepatocellular carcinoma. HCV patients frequently have kidney disorder, which is one of the most common extra-hepatic dysfunctions associated with HCV infection, appearing in 10% to 60% of patients [10].

The current study shows that ALT, AST, and total bilirubin in patients from Aswan were not significantly different from patients from Luxor.

Our results are supported by study of **Sanai *et al.* [11]** as they reported that the mean of ALT among their studied group was 33 (U/L) and the mean of AST was 28.1(U/L).

However, **Prasad *et al.* [12]** found that the mean of bilirubin among their patients was 0.9. But the level of ALT and AST doesn't not coincided with our results as they found that the mean of ALT was 135.1 (IU/L) and the mean of AST was 145.4 (IU/L).

The present study shows that the level of Hb was not statistically significantly different between groups.

Our results are in agreement with study of **Iliescu *et al.* [13]** as they observed that the mean of Hb of their cases was 12.9. According **Lawitz *et al.* [14]**, the mean of Hb of their studied group was 12.3.

Hepatitis C virus (HCV) infection is associated with numerous extrahepatic manifestations, including kidney disease. Typical kidney manifestations of HCV-MC include hypertension, proteinuria, microscopic hematuria, kidney failure and nephrotic syndrome [15].

In the current study there were no statistically significant differences between groups as regard to creatine and glucose.

Our results are supported by study of **Pérez de José *et al.* [16]** as they reported that the mean of creatine of their cases was 1.9 ±1.1. Furthermore, **Muñoz‐Gómez *et al.* [9]** found that the mean of creatine of their patients was 3.06 ± 0.8.

However, **Pockros *et al.* [8]** revealed that at baseline, median creatinine was 6.2 mg/dL, creatinine clearance was 18.1 mL/min, eGFR was 10.9 mL/min/1.73 m^2.

The present study shows that PC (%) in patients from Aswan was not significantly different from that in patients from Luxor.

Kao *et al.* [17] findings indicated that DAAs for HCV infection have comparable safety and efficacy in advanced-CKD patients and in patients without or with early CKD. Advanced-CKD patients are a specific patient population, difficult to treat. Since advanced-CKD or dialysis patients are older, sicker, and with multicomorbidities, they often have poor tolerability of IFN-based regimens. A previous meta-analysis showed DAAs-based antiviral therapies were effective and well tolerated in stage-4–5 CKD patients [18].

Other benefits of DAAs treatment for CKD patients include reducing the risk of renal function progression and liver disease progression, as well as improving patients' well-being. The evidence comes from a previous study showing that DAAs administered to patients with HCV-related glomerulonephritis achieved an 83% SVR, with subsequent improvement of serum creatinine and reductions in proteinuria [19]. **Saadoun *et al.* [20]** evaluated the response to DAA treatment in a prospective multicentre study that included five patients with kidney injury. Proteinuria decreased from 0.9 to 0.2 g in a 24-h urine test and hematuria disappeared in 80% of cases at week 24.

Limitations of this study include the small sample size and exclusion of patients with prior HCV treatment failure or with cirrhosis, both of which have historically had poorer response to therapy with IFN-based regimens and some DAA regimens. Therefore, this study does not provide guidance for CKD patients with much lower baseline hemoglobin levels, who might not tolerate even a small decrease. Continued study of this regimen is warranted to determine whether the safety findings in this study are generalizable to a larger number of patients.

CONCLUSION

Treatment with newer DAAs is effective and safe for the treatment of HCV infected chronic kidney disease patients, DAAs-based therapy is highly effective and well tolerated without any adverse impact on renal function in HCV-infected renal allograft recipients. Although initial results are promising, the long-term outcomes including breakthrough HCV replication and effect on progression of chronic liver disease are yet to be seen.

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