Impact of Direct Acting Antivirals Agents on kidney function in Hepatitis C Virus infected patients with chronic kidney disease

A Thesis

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By

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بسم الله الرحمن الرحيم
قالوا
سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم
صدق الله العظيم
سورة البقرة الآية: ٣٢

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Wedad Adel Mahmoud Abdo

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List of Abbreviations

Abbr.	Full-term
AASLD	**:** American Association for the Study of Liver Diseases
AKI	**:** Acute kidney injury
ALT	**:** Alanine aminotransferase
APRI	**:** Aminotransferase/ platelet ratio index
CD	**:** Cluster of differentiation
CKD	**:** Chronic kidney disease
DAAs	**:** Direct-acting antiviral agents
DAMPs	**:** Damage-associated molecular patterns
EASL	**:** European Association for the Study of the Liver
ER	**:** Endoplasmic reticulum
ESRD	**:** End-stage renal disease
FSGS	**:** Focal segmental glomerulosclerosis
GFR	**:** Glomerular filtration rate
HCC	**:** Hepatocellular carcinoma
HCV	**:** Hepatitis C virus
HD	**:** Hemodialysis
HIV	**:** Human immunodeficiency virus

HRS **:** Hepatorenal syndrome

HVPG **:** Hepatic venous pressure gradient

IDSA **:** Infectious Diseases Society of America

IFN **:** Interferon

INR **:** International normalized ratio

IRES **:** Internal Ribosome Binding Site

KDIGO **:** Kidney Diseases Improving Global Outcomes

KT **:** Kidney transplantation

MDRD **:** Modification of Diet in Renal Disease

MELD **:** Model for End-Stage Liver Disease

MPGN **:** Membranoproliferative glomerulonephritis

NK **:** Natural killer

NS **:** Nonstructural

NTPase **:** Nucleoside-triphosphatase

OMV/PTV/RTV Ombitasvir, Paritaprevir, and Ritonavir

PAMPs **:** Pathogen-associated molecular patterns

PAT **:** Parenteral anti-schistosomal therapy

PEG-IFN **:** Pegylated IFN

PLA2R **:** Phospholipase A2 receptor

Pr/Cr **:** Protein/creatinine

PrOD **:** Paritaprevir/ritonavir/ombitasvir plus dasabuvir

RAAS **:** Renin-angiotensin-aldosterone system

RBV **:** Ribavirin

RF **:** Rheumatoid factor

RNA **:** Ribonucleic acid

SRB **:** Scavenger receptor class B

SVR **:** Sustained virological response

TE **:** Transient elastography

TIPS **:** Transjugular intrahepatic portosystemic shunt

TLR **:** Toll-like receptor

TNF **:** Tumor necrosis factor

WHO **:** World health organization

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ABSTRACT

Introduction: Despite the significant link between HCV and CKD progression, most of the patients with CKD infected with HCV remain untreated, because they have historically been difficult to treat due to common adverse effects associated with interferon (IFN), ribavirin, and first generation protease inhibitors. Recently, there have been major advancements in the treatment of HCV with the development of new direct- acting antivirals (DAAs).

Objectives: To evaluate the safety and efficacy of DAAs and their impact on kidney function in CKD patients.

Patients and Methods: We conducted a prospective observational study on 100 CKD patients stages 3-4, receiving treatment for HCV at MASRI (faculty of Medicine Ain Shams University Research Institute), with two different DAAs regimens, completed over six months follow up. Kidney function was followed during and after treatment.

Results: Sustained virological response (SVR) was achieved in all patients. AKI (acute kidney injury) was uncommon; it occurred in three (3%) patients, out of them, two patients showed complete recovery. Adverse events were common (43%), but serious adverse events were uncommon (2%).Improvement of eGFR (8-15 ml/min/1.73 $m^{2)}$ and proteinuria was found in both study groups.

Conclusion: DAAs were effective and well- tolerated for HCV infected patients with stage 3-4 chronic kidney disease, where viral clearance caused improvement in eGFR and proteinuria.

Keywords: Hepatitis C virus (HCV), Direct-acting antiviral (DAA), Chronic kidney disease (CKD).

Introduction

Hepatitis C virus (HCV) affects over 70 million people worldwide, corresponding to 1.0% of the global population. Public interest in HCV is growing, especially since the virus can also induce extrahepatic manifestations (in 40–70% of cases) including autoimmunity-related symptoms, metabolic, renal, cardiovascular, central nervous system or lymphoproliferative disorders ***(Iliescu et al., 2020).***

The prevalence of HCV infection is highest in Egypt ranging from 6% to 40% with an average of 14%. This is greatly attributable to the era of parenteral anti-schistosomal therapy (PAT) mass- treatment campaigns between the period of 1960-1980 ***(El-Zanaty and Way, 2015).***

Hepatitis C virus (HCV) infection is strongly associated with chronic kidney disease (CKD). It is an independent risk factor for developing CKD, and significantly increases morbidity and mortality in patients with CKD ***(Shuster et al., 2019).***

It is well recognized that HCV infection can directly, via glomerulonephritis and cryoglobulinemic vasculitis, or indirectly, via hepatic cirrhosis and associated complications of portal hypertension, cause renal dysfunction and large-scale community observational studies have shown that HCV

infection increases the risk for incident chronic kidney disease (CKD) and progression to end-stage renal disease ***(Saxena &Terrault. 2016).***

Treatment for HCV infection has changed in the past few years with the introduction of direct-acting antiviral agents (DAAs) that have improved sustained virological response (SVR) compared with pegylated interferon–ribavirin (IFN ± RBV) , even in patients with chronic kidney disease (CKD) ***(Pérez de José et al., 2020).***

DAAs directly target viral proteins critical to HCV's replicative machinery and, when used in combination, produce cure rates of >97%. Despite of recent advances, little is known about the effect of HCV treatment with DAAs on short- or long-term kidney function. Whether or not the association of HCV with rapid CKD progression can be mitigated by HCV treatment has not yet been evaluated in the era of DAA therapies for HCV infection ***(Sise et al., 2020).***

In this context, HCV-infected patients with CKD stages 1 [glomerular filtration rate (GFR) > 90 mL/min 1.73 m^2], 2 (GFR 60–89 mL/min per 1.73 m^2), and 3a (GFR 45–59 mL/min per 1.73 m^2) should be considered to receive direct-acting antivirals (DAA), with the goal of slowing the progression of CKD. HCV-infected patients with CKD stages 3b (GFR 30–44 mL/min per 1.73 m^2), 4 (GFR 15–29 mL/min