

The effect of direct antiviral agents (DAAs) on glomerular filtration rate (GFR)

Thesis

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Internal Medicine**

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List of abbreviations

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Abb.	Full Term
Ag	Antigen.
AIN	Acute interstitial nephritis.
AKD	Acute kidney disease.
AKI	Acute kidney injury.
ALT	Alanin aminotransferase.
ANA	Anti nuclear antibody.
ASMA	Anti smooth muscle antibody.
AST	Aspartate aminotransferase.
C1q	Complement component 1q.
C3a	Complement component 3.
C4	Complement component 4.
C5a	Complement component 5a.
CHC	Chronic hepatitis c.
CKD	chronic kidney disease.
DAAs	Direct antiviral agents.
DCV	Daclatasvir.
DM	Diabetes mellitus.
E2	Envelope glycoprotein 2
eGFR	estimated Glomerular filtration rate.

List of abbreviations

ELISA	Enzyme linked immune sorbent assay.
ESKD	End stage kidney disease.
ESRD	End stage renal disease.
FDA	Food and drug administration.
FSGS	Focal segmental glomerulosclerosis.
GFR	Glomerular filtrating rate.
H&E	Hematoxylin and Eosin.
HCV	Hepatitis c virus.
HD	Hemodialysis.
HIV	Human immunodeficiency virus.
IFN	Interferon.
IgA	Immunoglobulin A.
IgG	Immunoglobulin G.
IgM	Immunoglobulin M.
LDV	Ledipasvir.
mg	Milligram.
Min	minute.
MPGN	Membrano-proliferative glomerulonephritits.
NS	Non-structural.
NS3/4A	Non-structural protein 3/4A.
NS3	Non-structural protein 3.
NS5A	Non-structural protein 5A.

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NS5B	Non-structural protein 5B.
NSAIDs	Non steroidal anti-inflammatory drugs.
PAN	Polyarteritis nodosa.
PAS	Periodic acid–Schiff stain
PCR	Polymerase chain reaction.
Peg-IFN	Pegylated interferon:
RBV	Ribvirin.
RCT	Randomized controlled trial.
RF	Rheumatoid factor.
RNA	Ribonucleic acid.
SIM	Simeprevir.
SR-B1	Scavenger receptor class B type 1.
SOF	Sofosbuvir.
SVR	Sustained virological response.
SVR12	sustained virological response 12 weeks after the end of therapy
TLR	Toll like receptor.

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ABSTRACT

Background: Hepatitis C virus (HCV) infection is known to be associated with high rates of liver related morbidities and mortality in the whole world. The interest of Public in HCV is growing, as more than 180 million people, (2.8%) of the global population, are infected with HCV.

Aim of the Study: To evaluate the effect of direct antiviral agents on glomerular filtrating rate (GFR).

Patients and Methods: The study performed on **120 subjects** from the Hepatology outpatient clinic at Sharque elmadinah Hospital in Alexandria.

Results: The current results showed that the mean decrease in GFR in patients who received SOF/DAC were 5.21 ± 15.57 and 6.18 ± 16.13 after full 12 week regimen and after 1 year respectively while the mean decrease in patients SOF/SIM were 4.35 ± 14.9 and 3.57 ± 13.08 respectively. The decrease was not statistically significant in both regimens. Moreover, the mean GFR decrease in the only patient received SOF/Ribavirin was 12.8 and 30.9 after 12 weeks regimen and after one year respectively while for the only patient who received PAR/OMB/Rito/Ribavirin the decrease was 5.5 and 53.4 respectively. unfortunately, due to lack of sufficient patients number, the decrease an not be expressed statistically.

- **Conclusion:** The new direct antiviral agents (sofosbuvir , daclatasvir and simeprevir) are effective and safe regarding glomerular filtration rate in patients with normal renal function. However, a meticulous monitoring of kidney function is mandatory during the course of these medications to early detect any untoward side effects. Moreover, such studies will yield beneficial data about the renal safety of these drugs if it could be performed on a larger scale of patients.

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Mohamed Hassan Abdelgawad Mohamed

Introduction

Hepatitis C virus (HCV) is major cause of acute hepatitis. After acute infection, approximately 50% to 70% of HCV patients develop chronic infection. HCV infects 170 million individuals approximately worldwide. Patients with Chronic hepatitis C infection are at high risk to develop life-threatening complications such as liver cirrhosis in 20% of cases and hepatocellular carcinoma (HCC). HCV is associated with many extrahepatic complications including glomerulonephritis, insulin resistance, type 2 diabetes mellitus. (**Li and Lo , 2015**).

Epidemiological studies showed that the risk of chronic kidney disease (CKD) is more than 20% higher in patients with HCV infection than in seronegative individuals (**Park *et al.*, 2015**). HCV infection increases the risk of end stage renal disease (ESRD) and increased risk of mortality (**Lee *et al.*, 2012**).

Patients with HCV infection have an increased risk of developing diabetes mellitus , hypertension and renovascular diseases (**Petta *et al.*, 2014**). Finally, chronic HCV infection is the most common viral infection seen in patients with renal insufficiency (**Kamar *et al.*, 2013**).

Introduction

The kidney is a major component of the HCV clinical syndrome; besides the liver, the immune system, the musculoskeletal system, the skin and hematopoietic system. This viral infection imposes itself as a cause of kidney disease, a major risk in hemodialysis units and a significant threat in kidney transplantation. (**Barsoum *et al.*, 2017**).

Chronic HCV infection is associated independently with the development of chronic kidney disease (CKD) (**Rogal *et al.*, 2016**) . A meta analysis that was published in 2015 showed that chronic HCV infection was associated with about 43% increase in the development of CKD and a 51% increase in the risk of proteinuria . (**Fabrizi *et al.*, 2015**). There is also a very high risk of progression to ESKD in patients with chronic HCV infection and CKD, and an increased risk of mortality in patients on dialysis (**Lee *et al.*, 2014**).

The emergence of direct-acting antivirals (DAAs) has brought HCV treatment into a revolutionized era. The rate of SVR at post-treatment week 12 (SVR 12) with undetectable HCV RNA was over 90–95% in the normal renal function subjects, with tolerable adverse events. (**Afdhal *et al.*, 2014**).

Aim of The Work

Aim of the work

The aim of this work is to evaluate the effect of direct antiviral agents on glomerular filtration rate(GFR) in HCV positive patients with normal renal function after the full treatment period (12weeks) and 1 year after the end of regimen.

Chapter 1

HCV Related kidney diseases

Epidemiology:

Hepatitis C virus (HCV) infection is known to be associated with high rates of liver related morbidities and mortality in the whole world. The interest of Public in HCV is growing, as more than 180 million people, (2.8%) of the global population, are infected with HCV. (**Thrift *et al.*, 2017**).

HCV infection leads to many complications -not only- hepatic complications such as hepatic decompensation, liver cirrhosis and hepatocellular carcinoma , but also extrahepatic complications that include autoimmune, renal, cardiovascular, metabolic, and lymphoproliferative disorders. (**Cacoub *et al.*, 2016**).

Epidemiological studies showed that the risk of chronic kidney disease (CKD) is more than 20% higher in patients with HCV infection than in seronegative individuals (**Park *et al.*, 2015**). HCV infection increases the risks of end stage renal disease

(ESRD (**Hsu *et al.*, 2015**) and renal mortality (**Lee *et al.*, 2012**). patients with HCV infection have an increased risk of developing diabetes mellitus , hypertension and renovascular diseases (**Petta *et al.*, 2014**).

Chronic HCV infection is the most common viral infection seen in patients with renal insufficiency (**Kamar *et al.*, 2013**). Kidney manifestations in particular are common extrahepatic complication of HCV infection. Chronic HCV infection is related directly to chronic kidney disease (CKD) and may accelerate renal deterioration, leading to end-stage renal disease (ESRD). (**Park *et al.*, 2018**).

The prevalence of hepatitis C virus (HCV) infection among hemodialysis (HD) patients has been reported to range from 10% to 25% .(**Roth *et al.*, 2011**).

HCV infection increases the rates of morbidity and mortality in both patients on dialysis and kidney transplant recipients. (**Scott *et al.*, 2010**).

Extrahepatic manifestations in patients with HCV infection:.

- Mixed cryoglobulinemia
- Cryoglobulinemic vasculitis
- B-cell Non hodgkin's lymphoma.
- Sicca syndrome
- Arthralgia and myalgia
- Autoantibody production (i.e. cryoglobulins , RF , and ANA, anticardiolipin, antithyroid and ASMA)
- Polyarteritis nodosa
- Monoclonal gammopathies
- Immune thrombocytopenia
- Diabetes mellitus type 2
- Insulin resistance
- Glomerulonephritis
- Renal insufficiency
- Fatigue
- Cognitive impairment
- Depression
- Impaired quality of life
- Polyarthrititis and fibromyalgia
- Cardiovascular disorders (i.e. stroke, ischemic heart disease).

(Cacoub *et al.*, 2016).