INTRODUCTION

Hepatitis C Virus (HCV) infection is a major global health challenge. It is estimated that more than 80 million people are chronically infected worldwide, with 3–4 million new infections and 350 000 deaths occurring each year because of HCV-related complications such as Cirrhosis and Hepatocellular Carcinoma **(*Gower et al., 2014)***

Overall, HCV prevalence between ranged, among blood donors between 5-25%, and among other general population groups between 0-40%. HCV prevalence among multi-transfused patients ranged between 10-55%, among dialysis patients between 50-90% ***(Mahamoud et al., 2013)***.

Infection with hepatitis C virus (HCV) is a common nosocomial occurrence among hemodialysis (HD) patients ***(Iwasa et al., 2014)***. It is considered a cause of end-stage liver disease and contributes to high mortality and morbidity among patients on maintenance dialysis ***(Ingsathit et al., 2013)***.

Patients with end-stage renal disease (ESRD) receive frequent blood transfusions to correct their chronic anemia. Transfusion of blood or blood products still constitutes an important route of transmission of HCV ***(Northcott et al., 2013)***.

Furthermore, the risk of contracting HCV infection is increased with the sharing of dialysis machines among patients.

Studies reported a reduction in the prevalence of HCV among HD patients by practicing standard infection control measures and the isolation of seronegative (anti-HCV negative) patients ***(Barril et al., 2013)***.

Screening for anti-HCV antibodies by EIA remains a simple method, but this type of test is only meaningful for ruling out HCV infection in ESRD patients in low-prevalence settings. One disadvantage of this serologic test is false-negative result, which can present challenges for distinguishing acute from chronic HCV infection. In a case where HCV infection is strongly suspected but the HCV antibody EIA is negative, blood testing for HCV RNA should be done directly using polymerase chain reaction technique ***(European Association for the Study of the Liver, 2011)***.

When EIA reveals that an ESRD patient is anti-HCV positive, the next step is quantitative determination of viral load. This helps confirm the antibody test result and is also useful for assessing the patient's prognostic risk stratification prior to antiviral treatment ***(European Association for the Study of the Liver, 2011).***

For more than a decade, treatment of HCV with pegylated interferon (pegIFN) plus ribavirin has been recommended but well-known treatment-limiting adverse effects, and contraindications to patients on regular dialysis have limited broad uptake of HCV treatment in patients. The

interferon-free, all-oral regimen of the 3 direct-acting antivirals Ombitasvir, Paritaprevir with ritonavir (HCV Protease Inhibitors; HCV Polymerase Inhibitors HCV NS5A Inhibitors) with or without Ribavirin is used now among patients on regular dialysis.

AIM OF THE WORK

To evaluate the efficacy and safety of *Ombitasvir*/*Paritaprevir*/*Ritonavir* with or without Ribavirin in treatment of chronic Hepatitis C Egyptian patients with End Stage Renal Disease on Regular Hemodialysis and compare it with the same treatment result in chronic Hepatitis C Egyptian patients with normal renal functions.

Chapter 1
HEPATITIS C VIRUS

Hepatitis C virus is grouped in the genus Hepacivirus within the family Flaviviridae. These viruses have a positive-sense RNA genome that contains one long open reading frame (ORF) flanked by highly structured non-translated regions (NTRs) that are essential for RNA replication ***(Todd et al., 2015).***

HCV is a small (50 nm) enveloped virus that was first isolated and cloned in 1989. It has a positive single–stranded RNA with approximately 9600 nucleotides and a genome composed of structural and nonstructural proteins ***(Jang and Chung, 2011).***

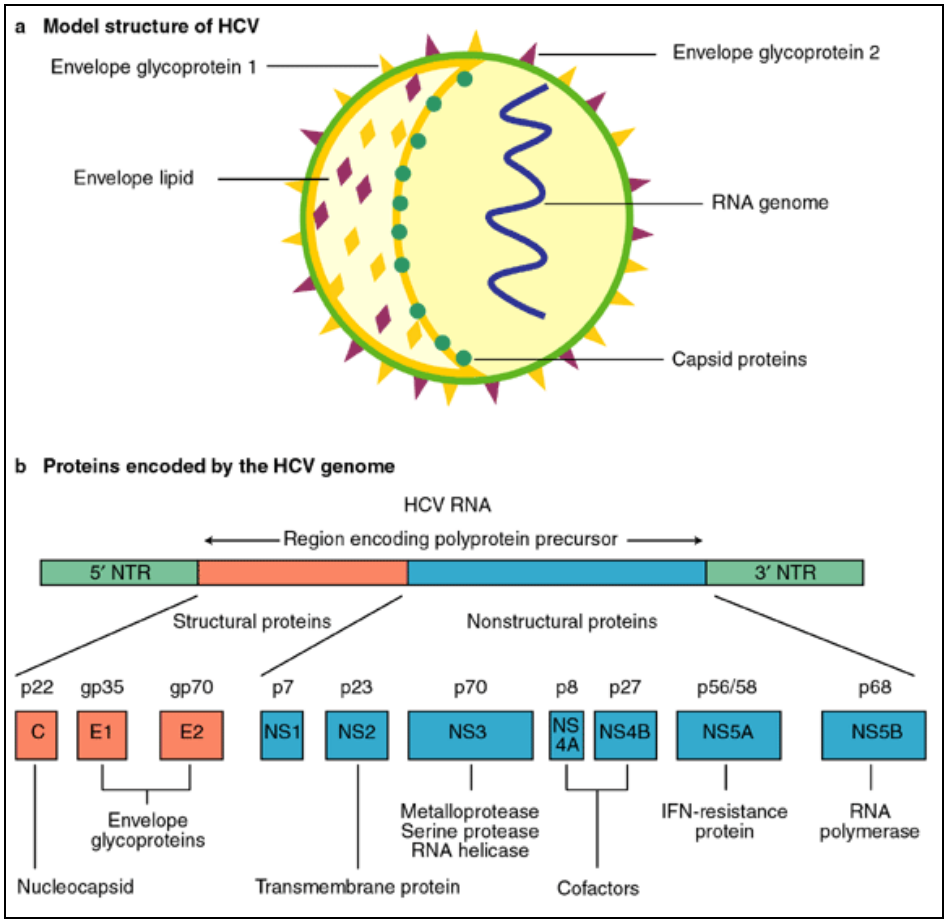

Figure (1): Hepatitis C virus (HCV): model structure and genome organization.

HCV strains are classified into seven recognized genotypes (1-7) on the basis of phylogenetic and sequence analyses of whole viral genomes. HCV strains belonging to different genotypes differ at 30-35% of nucleotide sites. Within each genotype, HCV is further classified into 67 confirmed and 20 provisional subtypes. Strains that belong to the same subtype differ at <15% of nucleotide sites ***(Smith et al., 2014).***

Globally, genotype 1 (G1) accounted for 46% of all anti-HCV infections among adults making it the most common, followed by G3 (22%), G2 (13%), G4 (13%), G6 (2%), and G5 (1%). Undefined or combination genotypes accounted for 3% of the total HCV infections. Genotype 1b was the most common sub-type, accounting for 22% of all infections. However, significant regional, country and local variations existed. Infections in North America, Latin America, and Europe were predominately G1 (62–71%) with G1b accounting for 26%, 39%, and 50% of all cases respectively. North Africa and the Middle East had a large G4 population (71%), which was attributable to the high prevalence of G4 in Egypt. When Egypt was excluded, genotype 4 accounted for 34% of all infections and the genotype distribution of this region was dominated by G1 (46%). Asia was predominately G3 (39%) followed by G1 (36%), largely driven by the HCV infections in India and Pakistan. G1b accounted for 25% of all infections in this region. In Australasia, G1 dominated (53%), followed by G3 (39%). G1b was present in 16% of cases ***(Gower et al., 2014).***

HCV Genotypes:

Hepatitis C virus has a high capability to generate mutations and exists as six different genotypes, subdivided into more than 60 subtypes. This constant variation of the HCV genome is the major reason for the difficulties encountered in the development of a vaccine against HCV ***(Nicolas et al., 2016).***

In a large retrospective literature analysis combining epidemiologic data from 1217 studies published between 1989 and 2013 and representing 117 countries. The study demonstrated that genotype-1 is the most predominant (42%) and followed by genotype-3 (30%) corresponds to approximately 23%, while genotype-5 represents less than 1% of the total number of HCV cases ***(Nicolas et al., 2016).***

Hepatitis C virus genotype-4 is prevalent among Middle East and Africa causing more than 80% of HCV infections and has recently spread to several European countries. Egypt has the highest prevalence of HCV worldwide and the highest frequency of HCV genotype-4 responsible for almost 90% of infections ***(Faisal et al., 2015).***

The response to therapy is also dependent on HCV genotype; genotype-1 and 4 infections are the most difficult to cure with peg-IFN-α and ribavirin combination therapy as compared to genotypes-2 and 3 ***(Nicolas et al., 2016).***

Egypt is believed to have the highest rate of hepatitis C in the world (estimated at >10%) and most other African countries have prevalence rates ranging from 2% to >3% ***(Amany et al., 2017).***

Hepatitis C virus (HCV) infection affects approximately 180 million individuals worldwide. In some countries, up to 75% of HCV patients are unaware of their disease due to the latent nature of disease progression ***(Smith et al., 2012).***

HCV in Egypt:

The prevalence of hepatitis C virus (HCV) infection in Egypt is the highest in the world. The high HCV prevalence is largely attributed to the parenteral antischistosomal therapy (PAT) campaigns conducted from the 1950s through the 1980s. In which 36 million injections were administered to >6 million people, almost all with unsterilized and shared syringes and needles. This represents the largest ever iatrogenic spread of blood-borne infection ***(Gomaa et al., 2017).***

In 1996, the HCV seroprevalence was > 40% among adults, whereas in 2008, the Demographic Health Survey (DHS) showed a seroprevalence of 14.7% and viremic prevalence of 9.7% in 15-59-year-old patients. ***(El-Zanaty F2009.)***

The latest DHS in 2015 reported a seroprevalence of 10% and viremic prevalence of 7% ***(El-Zanaty 2015).*** As per the DHS, the HCV burden significantly decreased approximately 30% between 2008 and 2015. However, in the 2008 DHS, this apparent decline in HCV seroprevalence was not attributed exclusively to the decrease in the newly acquired infections but to the aging of patients infected 50 years ago in the mass campaigns held for treatment of schistosomiasis ***(Kandeel et al,2017).***

Risk factors associated with HCV infection in Egypt

In 11 selected articles published between 2008 and 2013, which aiming to determine risk factors responsible for the high incidence and prevalence of HCV in Egypt. They categorized the risk factors into two major groups: "Unsafe medical practices and other risk factors". Unsafe medical practices included surgery, intravenous injections, dental intervention, stitches and catheterization. The other risk factors included illiteracy, maternal HCV and familial transmission ***(Tawhida et al., 2015).***

Figure (2): Timeline of hepatitis C virus prevalence in Egypt among adults.

Mode of Infection by HCV virus

1- Blood and blood products:

The most common way to get hepatitis C is through exposure to infected blood. Transfusion of blood contaminated with HCV is an important source of transmission. And not only associated with whole blood transfusion, but also transmitted

by blood products ***(Mark and Arnaud, 2014).*** Those receiving repeated blood transfusions are at particular risk as patients with haemophilia and thalassemia major ***(Atwa and Abdel Wahed, 2017).***

2- Intravenous drugs injection:

Injection drug use is the single most important mode of transmission of HCV in the United States and probably most western countries is the illicit use of injectable drugs, transmission through blood to blood contact, either via direct or indirect sharing of injecting equipment ***(Piyush et al., 2016).***

Most reports of HCV incidence in people who injected drugs fall into the range of 20–40 infections per 100 person yearly. However, incidence rates above and below this range have been recorded, with some of the highest rates observed

3- Haemodialysis:

Haemodialysis (HD) is a primary mode of therapy for patients with end stage renal disease (ESRD). The prevalence rates of HCV in the haemodialysis population vary between 4.3–45.2% ***(Jamil et al., 2016).***

Patients with end-stage renal disease (ESRD) receive frequent blood transfusions to correct their chronic anemia. Transfusion of blood or blood products still constitutes an important route of transmission of HCV ***(Northcott et al., 2013).***

Seroconversion may be associated with previous blood transfusion, central venous catheter use, switching between dialysis places, improper implementation of isolation procedures and infection control measures ***(Khodir et al., 2012).***

Furthermore, the risk of contracting HCV infection is increased with the sharing of dialysis machines among patients. Studies reported a reduction in the prevalence of HCV among HD patients by practicing standard infection control measures and the isolation of seronegative (anti-HCV negative) patients ***(Barril and Traver, 2013).***

4- Nosocomial and occupational exposure:

Hepatitis C virus (HCV) infection is a significant health problem in the United States and elsewhere. Hepatitis C infection presents risks for both nosocomial transmission to patients and occupational spread to health care workers. All known risk factors associated with nosocomial transmission of hepatitis C were carefully recorded, including: (1) Transfusion of blood products (2) Invasive procedures such as diagnostic endoscopy, therapeutic endoscopy, angiography and transcutaneous arterial embolization, other radiological procedures requiring intravenous contrast, liver biopsy, percutaneous ethanol injection, radiofrequency ablation, transhepatic cholangiography, hepatic hemodynamic studies and transcutaneous intrahepatic portosystemic shunt and large volume paracentesis (3) Minor and major surgical interventions. The transmission of infections to health workers

through percutaneous and mucocutaneous routes and documented through exposure to blood, body fluids and needle stick injuries in operation, delivery, emergency rooms and in laboratories ***(Muluken and Gedefaw, 2014).***

B- Non-parenteral transmission:

1- Vertical transmission:

Vertical transmission refers to viral transmission from the mother to the infant during pregnancy, at the time of delivery or during the first 28 days after birth. The mechanisms underlying vertical transmission of HCV are poorly understood ***(Erica et al., 2016).***

2- Sexual transmission:

The efficiency of hepatitis C virus (HCV) transmission by sexual activity remains controversial. It is not as common as it is with hepatitis B virus ***(Norah et al., 2013).***

Several studies have reported low rates of sexual transmission in HCV-serodiscordant heterosexual partners. In cross-sectional studies from Europe, the USA and Southeast Asia the prevalence rates of HCV among heterosexual couples have ranged from 0% to 27% ***(Denise et al., 2016).***

3- Household members (interfamilial transmission):

It is refers to transmission occurring between patients infected with HCV and their household members including

their immediate relatives and other individuals sharing the same house. But HCV is classically considered as poorly contagious within families ***(Cyrille et al., 2014).***

The possible route of infection in cases for which there are known family or household contacts may be an in apparent parenteral exposure, for example by contamination of broken skin with infected serum or blood or by sharing household objects such as razors and toothbrushes ***(Giuseppe et al., 2013).***

Overall, HCV prevalence between ranged, among blood donors between 5-25%, and among other general population groups between 0-40%. HCV prevalence among multi-transfused patients ranged between 10-55%, among dialysis patients between 50-90% ***(Mohamoud et al., 2013).***

Chapter 2
HCV AND KIDNEY

Renal involvement of hepatitis C virus infection was first reported two decades ago; however, knowledge of the association between HCV and low eGFR in the adult general population is limited and controversial. Hepatitis C virus infection is linked to CKD in several ways some forms of renal disease are precipitated by HCV infection, and patients with end-stage kidney disease are at increased risk of acquiring HCV ***(Mangia and Ripoli, 2013).***

Although the primary burden of disease is associated with advanced liver disease complications (e.g., cirrhosis, hepatocellular carcinoma and liver transplant), It is estimated that nearly half of HCV-seropositive patients are diagnosed to experience at least one extra-hepatic complication including dermatological, rheumatological and haematological disorders, as well as renal dysfunction **(*Razavi et al., 2013)*.**

A 70% higher risk of chronic kidney disease (CKD) (defined as an estimated glomerular filtration rate of <60mL/min/1.73m^2) has been observed in HCV seropositive patients compared with seronegative patients ***(Fabrizi et al., 2015).***