Assessment Of The Impact Of Obesity On Sustained Virologic Response To Sofosbuvir Based Regimens In Chronic Hepatitis C Patients.

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List of Abbreviations

AFP	Alpha Feto Protien
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CBC	Complete Blood Count
CHC	Chronic Hepatitis C
DAAs	Direct Acting Antivirals
Dac	Daclatasvir
DM	Diabetes Mellitus
ETR	End of Treatment Response
FDA	Food and Drug Administration
Hb	Hemoglobin
HCC	Hepato Cellular Carcinoma
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
INR	International Normalized Ratio
IR	Insulin Resistance
Led	Ledipasvir
MS	Metabolic Syndrome
NAFLD	Non Alcoholic Fatty Liver Disease
RBG	Random Blood Glucose
Rib	Ribavirin
Sim	Simeprevir
Sof	Sofosbuvir
SVR	Sustaind Virologic Response
T2DM	Type 2 Diabetes Mellitus
TGs	Tri Glycerides
WBCs	White Blood Cells
WHO	World Health Organization

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Introduction

Globally, it was estimated that in 2016, total HCV prevalence is 2.5% more than 177.5 million of HCV infected adults, with a global viraemic rate of 67% ***(Arnolfo et al.,2016)***.

Egypt has the largest epidemic of HCV in the world. The prevalence of HCV in Egypt is 14.7%. HCV kills an estimated 40 000 Egyptians a year and at least 1 in 10 of the population aged 15 to 59 is infected ***(WHO, 2014)***.

Hepatitis C virus can cause both acute and chronic hepatitis. Chronic HCV infection often follows a progressive course over many years and can ultimately result in cirrhosis, hepatocellular carcinoma, and the need for liver transplantation ***(Chopra et al., 2015)***.

Antiviral therapy is the cornerstone of treatment of chronic hepatitis C virus infection. The goal of antiviral therapy in patients with chronic HCV is to eradicate HCV RNA, which is predicted by attainment of a sustained virologic response (SVR). SVR is associated with a 97 to 100 percent chance of being HCV RNA negative during long-term follow-up ***(Swain et al., 2010).***

Attainment of SVR has been associated with decreases in all-cause mortality, liver-related death, need for liver transplantation, hepatocellular carcinoma rates, and liver-related

complications, even among those patients with advanced liver fibrosis ***(Morgan et al., 2013)***.

Several factors, both viral and host mediated, have been shown to be partially responsible for the failure rate to antiviral treatment regarding interferon-based therapies. Traditional predictors of response to interferon-based HCV therapy were: Patient factors that were associated with worse response to interferon-based therapy included male gender, older age, high body mass index (BMI), advanced liver fibrosis, history of failed treatment, black race, non-CC IL28B genotype, and the presence of certain comorbid conditions, such as HIV coinfection, insulin resistance, or diabetes. Viral factors that were associated with worse response included non-genotype-2 infection, high viral load, and unfavorable viral kinetics during treatment (eg, slow decline or rebound in viral level). These factors played a prominent role in management decisions ***(David et al., 2018)***.

Worldwide in 2014, 39% of adults aged 18 or more were overweight (BMI ≥ 25 kg/m2) (39% of men and 40% of women) and 13% were obese (BMI ≥30 kg/m2) (11% of men and 15% of women). Thus, nearly 2 billion adults worldwide are overweight and, of these, more than half a billion are obese ***(WHO, 2014)***.

Aim of the work:

To assess the impact of obesity on the SVR to sofosbuvir based therapy in patients with chronic HCV infection.

Review of Literature

Chronic hepatitis C infection

Hepatitis C virus (HCV) non-A, non-B hepatitis virus is related to flaviviruses. Its genetic organization and protein products classify it in the Flaviviridae family, while its diversity classified HCV as a separate genus (***Choo et al., 1989***).

HCV genotypes : Six major genotypes of HCV have been defined and More than 50 subtypes; the most common subtypes are 1a, 1b, 2a, and 2b (***Simmonds et al., 2005***).

However the evolution of genotypes has probably been influenced by several factors including immune selection, replication efficiency, infection patterns, geographic distribution of HCV genotypes, and population migration .

Genotype 1 is most common (60 to 70 percent of isolates) in the United States and Europe; genotypes 2 and 3 are less common in these areas, while genotypes 4, 5, and 6 are rare.

Genotype 3 is most common in India, the Far East, and Australia.

Genotype 4 is most common in Africa and the Middle East.

Genotype 5 is most common in South Africa.

Genotype 6 is most common in Hong Kong, Vietnam, and Australia (***Lau et al***., ***1996***).

Viral genotypes have a significant effect upon the clinical, pathological presentation of HCV and response to antiviral therapy (***Martinot et al., 1995***) **.**

Epidemiology : According to a recent systematic review of HCV epidemiological studies , published between 2000 and 2015, total global HCV prevalence was estimated 2.5% (177.5 million HCV infected adults), ranging from 2.9% in Africa and 1.3% in Americas, with a global viraemic rate 67% (118.9 million HCV RNA positive cases), varying from 64.4% in Asia to 74.8% in Australia. HCV genotype 1 is the most prevalent worldwide (49.1%), followed by genotype 3 (17.9%),4 (16.8%) and 2 (11.0%). Genotypes 5 and 6 are responsible for the remaining < 5%. This analysis suggests that HCV prevalence and the viraemic rate have decreased from 2005 to date (***Arnolfo et al., 2016***)**.**

The epidemiology of hepatitis C virus in Egypt: In a systematic review analyzed data from The Demographic Health Survey (DHS) of 2008 and that of 2015 **Elgharably et al** demonstrated that The Demographic Health Survey (DHS) of 2008 showed a national seroprevalence of 14.7% among those aged between 15 and 59 years, with viremic prevalence of 9.7% was higher in males than in females in all age groups. InThe DHS of 2015 included the age groups 1–59 years.The seroprevalence in the age groups 15–59 years was 10% (compared to 14.7% in the 2008 DHS), and the viremic prevalence to 4.4% (7% in the age groups 15–59 years and 0.2% in those aged <15 years).Estimation of the current and the future burden of HCV in Egypt by applying

different treatment scenarios using Markov model using Egyptian DHS 2008 datam shows that patients with cirrhosis are expected to increase from 750,000 cases in 2015 to peak to 925,000 cases by 2022 and then slightly decrease to reach 800,000 cases by 2030. By increasing the rate of treatment to 8% (treating 300,000–450,000 patients), the expected total viremic HCV cases will reach 1,000,000 cases by 2030, liver-related deaths will be <15,000 deaths and the number of patients with cirrhosis will decline by 87% to reach ~100,000 cases by 2030 (***Elgharably et al., 2017***). HCV incidence ranged from 0.8 to 6.8 per 1,000 person-years. HCV prevalence among pregnant women ranged between 5-15%, among blood donors between 5-25%, while among other general population groups between 0-40%. HCV prevalence among multi-transfused patients ranged between 10-55%, while among dialysis patients between 50-90%, and among other high risk populations between 10% and 85%. Risk factors appear to be parenteral anti-schistosomal therapy, injections, transfusions, and surgical procedures. Results of some researches suggest that there is no evidence of a statistically significant decline in HCV prevalence in both the general population (p-value: 0.215) and high risk population (p-value: 0.426) (***Mohamoud et al., 2013***).

Transmision :

The majority of patients infected with HCV in the United States and Europe was infected through intravenous drug use or blood transfusion, the latter mode of transmision has become rare since routine testing of the blood supply for HCV was started in 1990(***Nelson et al, 2011***). Other types of parenteral exposure in specific regions in the world as in Egypt was the epidemic caused by iatrogenic transmission during the era of parenteral-antischistosomal-therapy mass-treatment (***Frank et al., 2000***).

Clinical presentation of HCV infection :

Hepatitis C virus can cause both acute and chronic hepatitis. The acute process is self-limited, but rarely causes hepatic failure, usually the acute process progresses to chronic infection. Chronic HCV infection may be complicated by cirrhosis, hepatocellular carcinoma, and the need for liver transplantation (***Chopra et al., 2015***).

A- Acute hepatitis C :

Acute hepatitis C virus infection refers to the presence of clinical signs or symptoms of hepatitis within six months of presumed HCV exposure (***Blackard et al., 2008***). Patients with acute HCV are typically asymptomatic (***CDC, 2012***).