Impact of Diabetic Control on Achieving Sustained Virologic Response in Chronic HCV Patients Receiving Direct-Acting Antivirals

Thesis

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تأثير ضبط مستوي السكر بالدم علي تحقيق الإستجابة الفيروسية المستدامة في مرضي الالتهاب الكبدي المزمن فيروس "سي" عند تلقي العلاج بمضادات الفيروس المباشرة

رسالة

توطئة للحصول علي درجة الماجستير فى الباطنة العامة

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Contents

List of Abbreviations

AASLD	:	American Association for the Study of Liver Diseases.
AFP	:	Alpha feto protein.
ALP	:	Alkaline phosphatase.
ALT	:	Alanine aminotransferase.
ADA	:	American Diabetes Association.
APOB	:	Apolipoprotein B.
AST	:	Aspartate aminotransferase.
B-cells	:	Beta cells of the pancreas.
BMI	:	Body mass index.
CrCl	:	Creatinine clearance.
DAAs	:	Direct acting anti-viral agents.
DCV	:	Daclatasvir.
DM	:	Diabetes mellitus.
EASL	:	European Association for the Study of the liver.
ECG	:	Electrocardiography.
ECM	:	Extracellular matrix.
ELISA	:	Enzyme-linked immune sorbent assay.
ER	:	Endoplasmic reticulum.
ETR	:	Early treatment response.
FBS	:	Fasting blood sugar.
GGT	:	Gamma glutamyl transpeptidase.
GLUT4	:	Glucose transporter type 4.
HAART	:	Highly active antiretroviral therapy.
HbA1c	:	Glycosylated hemoglobin.
HBsAg	:	HBV surface antigen.
HBV	:	Hepatitis B virus.
HCC	:	Hepatocellular carcinoma.
HCV	:	Hepatitis C virus.
HCV-4	:	Hepatitis C virus genotype 4.
HDL	:	High-density lipoprotein.
HIV	:	Human immunodeficiency virus.
HOMA-IR	:	Homeostatic Model Assessment of Insulin

		Resistance.
HSC	:	Hepatic stellate cells.
IFG	:	Impaired fasting glucose.
IGF	:	Insulin-like growth factor.
IGF-1R	:	IGF-1 receptor.
IGF-BPs	:	IGF-binding proteins.
IGT	:	Impaired glucose tolerance.
INF	:	Interferon.
INR	:	International normalized ratio.
IR	:	Insulin resistance.
IRS	:	Insulin receptor substrate.
IRS-1	:	Insulin receptor substrate 1.
LDLs	:	Low-density lipoproteins.
LFT	:	Liver function tests.
MAPK	:	Mitogen-activated protein kinase.
MiR-122	:	MicroRNA-122.
NANHES-III	:	Third National Health and Nutrition Examination Survey.
NCCVH	:	National Committee for Control of Viral Hepatitis.
NK	:	Natural killer.
OGTT	:	Oral Glucose Tolerance Test.
PCR	:	Polymerase chain reaction.
PEG-IFN	:	Pegylated interferon.
PI3K	:	Phosphoinositol-3-kinase.
PPBS	:	Post-prandial blood sugar.
RASs	:	Resistance-associated substitutions.
RBV	:	Ribavirin.
ROS	:	Reactive oxygen species.
RVR	:	Rapid virological response.
SIM	:	Simeprevir.
SOF	:	Sofosbuvir.
SVR	:	Sustained virological response.
T2D	:	Type 2 diabetes.
VLDLs	:	Very-low-density lipoproteins.
WHO	:	The World Health Organization.

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Abstract

Aim of the work: the current study examined effect of diabetic control on achieving sustained virologic response (SVR) in chronic hepatitis C virus (HCV) patients who received Direct-Acting Antivirals (DAAs) (Daclatasvir (DCV)+ Sofosbuvir (SOF)± Ribavirin (RBV) for 12 weeks) according to the recommendations of The Egyptian National Committee for Control of Viral Hepatitis (December 2016). **Patients and methods**: this study was conducted in the Gastroenterology and Hepatology Unit, Internal Medicine Department, Ain Shams University Hospital. It was included 100 patients with chronic HCV infection (Treatment naive patients) (Child's A patients). All patients were subjected to history taking, through clinical examination, laboratory investigations, abdominal ultrasonography and calculation of FIB-4 score. Patients were classified in to 3 groups according to diabetic control. PCR for HCV RNA was assessed at 12 weeks post-treatment to evaluate SVR**. Results:** our results revealed that diabetic control seemed not to reduce SVR to DAAs (DCV + SOF ± RRV for 12 weeks) in chronic HCV infected patients. Overall, SVR was achieved by 91% of the 100 patients including 91.8% of patients treated with SOF+DAC and 89.7% of those treated with SOF+DAC+RBV.

Conclusion: our results showed that DCV + SOF ± RBV combination for 12 weeks is an effective and well tolerated regimen for patients with chronic HCV (treatment naive patients) (Child's A patients). Overall SVR of 91%.has been achieved. Also, diabetic control seems not to affect SVR sates in these patients. Although the management of metabolic alterations remains a relevant strategy to limit liver disease progression, the optimization of virologic response to DAAs based regimens should focus on factors other than diabetic control.

Keywords: hepatitis C, type-2 DM, diabetic control, direct-acting antivirals

Introduction

Hepatitis C virus (HCV) infection is a major health problem. The World Health Organization (WHO) estimates that at least 150-170 million people are chronically infected ***(Desbois and Cacoub, 2017)***. Approximately 25% of patients with chronic HCV hepatitis will develop cirrhosis, and a significant proportion will go on to develop hepatocellular carcinoma (HCC) ***(Lavanchy, 2009)***. Egypt has the highest prevalence rate of HCV in the world ***(Razavi et al., 2014)***, making it the most challenging public health problem facing the country. Studies show that 14.7% of the Egyptian population carries HCV-antibodies and 10% have an active infection with predominance of genotype 4 (about 93.1% of cases) ***(Gower et al., 2014)***.

Eradication of HCV infection can prevent histological deterioration ***(George et al., 2009)*** and causes significant reduction in liver-related morbidity and mortality ***(Cardoso et al., 2010)***. Optimal therapy for patients with hepatitis C virus genotype 4 (HCV-4) infection is changing rapidly; the standard of care for a long time has been a combination of pegylated interferon (PEG-IFN) and ribavirin (RBV), with modest response rates and considerable adverse events ***(Abdel-Razek and Waked, 2015)***. Since the introduction of direct acting anti-viral agents (DAAs) e.g: Sofosbuvir (SOF), Simeprevir (SIM), and Daclatasvir (DCV), the duration of treatment has been significantly shortened and response rates have increased with substantial

improvements in the side effect profiles ***(Eletreby et al., 2016) (Elsharkawy et al, 2017)***.

Hepatitis C virus infection has been shown to be linked to a higher prevalence of type 2 diabetes (T2D). This association is due to Beta cells of the pancreas (B-cells) dysfunction in the stage of chronic hepatitis which becomes more advanced with the development of liver cirrhosis ***(Elkarmouty et al, 2002)***, together with insulin resistance (IR) that occurs early in the course of the disease even in patients without or with minimal fibrosis. The mechanisms for HCV-induced IR are only partly understood and include a direct inhibitory effect of HCV on insulin signaling pathway. Insulin resistance in chronic HCV results in an increased rate of progression of hepatic fibrosis, cirrhosis and HCC ***(Hammerstad et al., 2015)***. Most studies found that IR reduces the response rate to PEG-IFN therapy. Whether IR affects the response to the new DAAs based regimens is still unknown ***(Bose and Ray, 2014) (Knobler and Malnick, 2016)***.

Aim of the work

The main aim of this study was to evaluate the effect of diabetic control on achieving sustained virologic response in chronic HCV patients receiving direct-acting antivirals (Daclatasvir + Sofosbuvir ± Ribavirin for 12 weeks).

Hepatitis C virus (HCV) & Direct acting antivirals (DAAs)

HCV prevalence

Global prevalence of HCV infected individuals based on positivity for anti-HCV antibodies has been estimated at 1.6% (range: 1.3–2.1%), that corresponds to 115 million (range: 92–149 million) people worldwide ***(Gower et al., 2014).*** However, not all of these people are currently infected with HCV; some have cleared the virus either spontaneously or due to treatment. Thus, the global viraemic prevalence (being positive for HCV RNA) is lower and estimated at 1% (range: 0.8–1.14%) or 71 million (range: 62–79 million) people worldwide. These estimates are based on extrapolations from 100 countries where generalizable studies have been conducted. (***The Polaris Observatory HCV Collaborators, 2017) (Manns et al., 2017).***

Prevalence of HCV infection is variable across the globe (Fig. 1). Egypt, Cameroon, Gabon, Georgia, Nigeria and Uzbekistan ***(Gower et al., 2014)*** all have an anti-HCV antibody prevalence of >5% in the adult population; iatrogenic infection is a key risk factor in these countries. The source of HCV infection in Egypt is well documented and attributed to intravenous treatment for schistosomiasis in the 1960–1970s ***(Arafa et al., 2005).***