Effect of Using Direct Acting Anti-Virals in Treatment of HCV Naive Patient with and without Portal Hypertension

Thesis

Submitted for partial fulfillment of master degree in Internal Medicine

By

Ahmed Reda El Husseiny Ali El Sabagh

M.B.B.Ch, Ain Shams University

Supervised by

Prof. Dr. / Khaled Zakaria Al Karmouty

Professor of Internal Medicine and Gastroenterology

Faculty of Medicine - Ain Shams University

Asst. Prof. Dr. / Eslam Safwat Mohamed

Assistant Professor of Internal Medicine and Gastroenterology

Faculty of Medicine - Ain shams University

Dr. Heba Ahmed Fahim

Lecturer of Internal Medicine and Gastroenterology

Faculty of Medicine - Ain shams University

Faculty of Medicine

Ain Shams University

2019

أثر استخدام مضادات الفيروسات المباشرة في علاج مرضي الالتهاب الكبدي الفيروسي سي الذين يتلقون العلاج لأول مرة في وجود ارتفاع ضغط الوريد البابي و عدم وجوده

رسـالة

توطئة للحصول علي درجة الماجيستير في أمراض الباطنة العامة

مقدمة من

الطبيب / أحمد رضا الحسيني علي الصباغ

بكالوريوس الطب والجراحة

كلية الطب - جامعة عين شمس

تحت اشراف

أ.د/ خالد زكريا القرموطي

أستاذ الباطنة العامة والجهاز الهضمى

كلية الطب - جامعة عين شمس

أ.م.د/ إسلام صفوت محمد

استاذ مساعد الباطنة العامة و الجهاز الهضمى

كلية الطب - جامعة عين شمس

د/ هبة أحمد فهيم

مدرس الباطنة العامة والجهاز الهضمى

كلية الطب - جامعة عين شمس

كلية الطب

جامعة عين شمس

٢٠١٩

سورة البقرة الآية: ٣٢

Acknowledgement

First and foremost thanks to ALLAH, the Most Merciful.

I wish to express my deep appreciation and sincere gratitude to ***Prof. Dr. / Khaled Zakaria Al Karmouty,*** *Professor of Internal Medicine and Gastroenterology, Ain Shams University, for his close supervision, valuable instructions, continuous help, patience, advices and guidance. He has generously devoted much of his time and effort for planning and supervision of this study. It was a great honor to me to work under his direct supervision.*

I wish to express my great thanks and gratitude to ***Asst. Prof. Dr. / Eslam Safwat Mohamed.*** *Assistant Professor of Internal Medicine and Gastroenterology, Ain Shams University, for his kind supervision, indispensable advice and great help in this work.*

I wish to express my great thanks and gratitude to ***Dr. Heba Ahmed Fahim.*** *Lecturer of Internal Medicine and Gastroenterology, Ain Shams University, for her kind supervision, indispensable advice and great help in this work.*

Last and not least, I want to thank all my family, my colleagues,, for their valuable help and support.

Finally I would present all my appreciations to my patients without them, this work could not have been completed.

Contents

Subjects
Page

List of Abbreviations

ALT	:Alanine amino-transeferase
apoE	:Apo-lipoprotien e
APRI	:Aspartate aminotransferase to platelet ratio index
AST	:Aspartate amino-transferase
CLA	:Chemiluminesence immunoassay
cLD	:Cytoplasmic lipid droplets
CT	:Computed tomography
DAAs	:Direc acting anti-viral drugs
DGAT	:Diacylglycerol acyltransferase
DM	:Diabetes mellitus
DNA	:Deoxy-ribo nucleic acid
EASL	:European association for study of liver
EDHS	:Egypt demographic and health survey
eGFR	:Estimated glomerular filtration rate
EGFR ER	:Epidermal growth factor receptor
EHIS	:Egyptian health issue survey
ELISA	:Enzyme linked immunosorbent assay
ELISA	:Endoplasmic reticulum
FDA	:Food and drug administration
FIB4	:Fibrosis-4
GT	:Genotype
HAV	:Hepatitis a virus
HB	:Haemoglobin
HBA1c	:Glycated haemoglobin
HBV	:Hepatitis b virus
HCC	:Hepato-cellular carcinoma
HCV	:Hepatitis c virus
HIV	:Human immunodeficiency virus
HSC	:Hepatic stellate cells
HTN	:Hypertension
HVPG	:Hepatic venous pressure gradient
INR	:International randomized ratio
LDL	:Low density lipoproteins
MRI	:Magnetic resonance imaging
NAT	:Nucleic acid test
NIs	:Neocleotide inhibitors
NNIs	:Non-nucleotide inhibitors
NO	:Nitrous oxide

NS	:Non-structural
PCR	:Polymerase chain reaction
PegINF	:Pegylated interferon
PLT	:Platelets
RAS	:Rennin angiotensin system
RBV	:Ribavirin
RIBA	:Recombinant immunoblot assay
RNA	:Ribo-nucleic acid
SVR	:Sustained virologic response
TLR4	:Toll-like receptor 4
VEGF	:Vascular endothelial growth factor
VLDL	:Very low density lipoproteins
WCC	:White cell count
WHO	:World health organization

List of Table

List of Figures

ABSTRACT

Background: Hepatitis C Virus (HCV) infection is a major global health challenge; it is estimated that more than 80 million people are chronically infected worldwide**.** Egypt has the highest prevalence of HCV in the world (predominantly genotype 4) secondary to the previous schistosomiasis eradication campaigns with very high incidence rates among elderly, rural areas and in lower social classes.

However, several oral anti-HCV drugs (direct acting antivirals; DAAs) have been developed over the last several years. Now, HCV can be eliminated from the infected host within 12 wk of DAA combination therapy without noticeable side effects

Aims: to evaluate the Effect of presence of portal hypertension on the results of treatment of chronic HCV infected naive patient with direct acting antivirals

Patients and methods:

200 subjects were divided into 2 groups: group I: including 100 cirrhotic patients with HCV infection and portal hypertension, group II: including 100 cirrhotic patients with HCV infection without portal hypertension.

Diagnosis of portal hypertension was confirmed by presence of esophageal varices in endoscopy.

Both group received combination of IFN-free DAAs**.**

Results: CK-18 was significantly elevated in patients of group I in comparison to group II, with mean ± SD: 460 ± 279, 167 ± 56 and 149 ± 57, respectively, and *P* value: 0.001. with mean ±SD: 59.6± 28, when compared with control group (with 23±8) *P* value < 0.001. ROC curve between Cases and Control as regards CK18 with Area Under the Curve (AUC): 0.925. Cutoff > 30 ug/l With Sensitivity: 86.67% & Specificity: 83.33%.. Ck-18 was found to be correlated with steatosis and fibrosis assessed by fibroscan with P value< 0.001.

Conclusion: treatment of 200 patients with HCV and compensated cirrhosis, HCV eradication reduced risk for liver decompensation, regardless of whether the patients had EVs.

Keywords: Oesophagus, Bleeding; Long-Term Outcome; Portal Pressure, HCV, cirrhosis.

INTRODUCTION

Worldwide it is estimated that 185 million people are chronically infected with Hepatitis C virus (HCV), with 3-4 million new infections per year and over 350,000 deaths due to HCV-related liver disease each year ***(Gower et al., 2016)***. The long term impact of HCV infection is highly variable, ranging from minimal effects to chronic hepatitis, advanced fibrosis, cirrhosis, decompensated cirrhosis and hepatocellular carcinoma. Chronic HCV infection may also induce severe extra-hepatic complications ***(Maasoumy and Wedemeyer, 2016).***

The goal of therapy is to eradicate HCV in order to prevent hepatic and extra-hepatic complications and to improve overall survival ***(Lavanchy, 2011).*** Advances in the treatment of HCV infection have demonstrated over 90% cure rates, as defined by the sustained virologic response (SVR), i.e. undetectable HCV RNA 12 weeks (SVR12) or 24 weeks (SVR24) after the end of therapy, as assessed by a sensitive molecular method with a lower limit of detection ≤15 IU/ml. Both SVR12 and SVR24 have been accepted as endpoints of therapy by regulators in the USA and Europe, given that their concordance is 99%. Long-term follow-up studies have shown that an SVR corresponds to a definitive cure of HCV infection in more than 99% of cases ***(Poiteau et al., 2016).***

This endpoint, which is associated with significant clinical benefits, was achieved only in 45-55% of patients who received a 24-48 week course of Pegylated Interferon (PegIFN) and Ribavirin (RBV) ***(Chevaliez et al., 2016)***, but is now obtained in 90% of patients treated with direct-acting antiviral drugs (DAAs), which are designed to target key steps in the HCV replication ***(Martinot-Piegnoux et al., 2015)***.

DAAs can be divided into 3 classes defined by the Non Structural (NS) HCV protein they target: NS3 Protease inhibitors, NS5B Polymerase inhibitors and NS5A protein inhibitors ***(Swain et al., 2015)***. The high efficacy, combined with the near perfect safety profile of DAAs, has challenged the need for regular on treatment monitoring of efficacy and safety, a feature that was one of the mainstays of PegIFN based
regimens ***(Asselah et al., 2016)***.

In light of the advances in HCV therapy, simplification of diagnosis confirmation, pre-treatment diagnostic workup and treatment monitoring is required to ensure broad access to these new therapies. Introduction of these highly potent therapies has obviated the need for response-guided therapy and reduced the role of treatment monitoring with highly sensitive quantitative HCV RNA tests ***(Chevaliez et al., 2016).***

Concerning portal hypertension, SVR was associated with a statistically significant yet modest decrease in hepatic venous pressure gradient (HVPG) 6 mo after INF-based therapy. In a small study including 8 patients who achieved SVR with antiviral triple therapy there was a significant decrease in both HVPG and liver stiffness 24 wk after therapy (10.3 mmHg *vs* 6.1 mmHg and 21.3 kPa *vs* 6.4 kPa, $P < 0.001$), with 5 patients (62.5%) achieving an HVPG < 6 mmHg. Indirect markers of portal hypertension such as platelet countand spleen size were also shown to improve after HCV eradication in INF-treated cirrhotic patients***(Lebanio et al., 2017).***

Concerning clinical endpoints after HCV eradication, a prospective study with 12 years follow-up showed a lower incidence of esophageal varices in Child A cirrhotic patients with SVR (0% *vs* 32%-39% in the untreated/non-SVR group). A lower incidence of *de novo* esophageal varices was also reported in cirrhotic patients who achieved SVR, although the progression of variceal size was not statistically different in patients with and without SVR, supporting the concept of the point of no return. Another prospective study also showed that SVR was associated with a lower incidence of *de novo* esophageal varices in cirrhotic patients treated with PEG-INF and (RBV) (HR = 0.23, 95%CI: 0.11-0.48), although it was not associated with a decrease in variceal progression or liver