Evaluation of Different Regimens of New Direct Acting Antiviral drugs (DAAs) for treatment of Recurrent Hepatitis C Virus Infection after Liver Transplantation

Thesis

Submitted for partial fulfillment of M.D degree Of Tropical Medicine

Presented by

Mostafa Abdelfattah Shamkh Ahmad

MB BCh , M.Sc - Ain Shams University

Supervised by

Prof. Dr. Mohga Ali Reda

Professor of Tropical Medicine

Faculty of Medicine, Ain Shams University

Prof. Dr. Mohammed Mohammed Bahaa

Professor of general surgery and liver transplantation

Faculty of Medicine, Ain Shams University

Prof. Dr. Iman Mohammed Fawzy Montasser

Assistant professor of Tropical Medicine

Faculty of Medicine, Ain Shams University

Faculty of Medicine

Ain Shams University

2018

تقييم النظم المختلفة لمضادات الفيروسات الجديدة ذات التأثير المباشر □عدوى التهاب الكبد الفيروسى ج المرتجعة بعد زراعة الكبد فى علاج

رسالة

توطئة للحصول علي درجة الدكتوراة في طب المناطق الحارة

مقدمة من

مصطفى عبد الفتاح شمخ أحمد/الطبيب

ماجستير طب المناطق الحارة – بكالوريوس الطب و الجراحة

تحت إشراف

□أ.د/ مهجة على رضا

أستاذ طب المناطق الحارة

كلية الطب- جامعة عين شمس

أ.د/ محمد محمد بهاء

أستاذ الجراحة العامة وزراعة الكبد

كلية الطب- جامعة عين شمس

□أ.د/ إيمان محمد فوزى منتصر

أستاذ مساعد طب المناطق الحارة

كلية الطب- جامعة عين شمس

كلية الطب

جامعة عين شمس

□٢٠١٨

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. Mohga Ali Reda****, Ain Shams University, for her close supervision, valuable instructions, continuous help, patience, advices and guidance. She has generously devoted much of her time and effort for planning and supervision of this study. It was a great honor for me to work under her direct supervision.*

I wish to express my great thanks and gratitude to ***Prof Dr.Mohammed M. Bahaa****, Ain Shams University, for his kind supervision, indispensable advice and great help in this work.*

Words fail to express my sincere appreciation, great gratitude to ***Prof. Dr. Iman Fawzy Montasser,*** *Assistant Professor of Tropical Medicine Department, Ain Shams University, whose continous supervision, advice and fruitful criticism have been of great help in performing this work.*

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

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

Contents

List of Abbreviations

2D regimen	**:**	Ombitasvir and paritaprevir (+ritonavir)
3D regimen	**:**	Ombitasvir, paritaprevir (+ritonavir) and dasabuvir
AASLD	**:**	American association for the study of liver diseases
ACR	**:**	Acute cellular rejection
AFP	**:**	Alpha feto protein
AIDS	**:**	Acquired immunodeficiency syndrome
AIH	**:**	Autoimmune hepatitis
AKI	**:**	Acute kidney injury
ALF	**:**	Acute liver failure
ALP	**:**	Alkaline phosphatase
ALT	**:**	Alanine aminotransferase
AS	**:**	Anastomotic stricture
ASCOT	**:**	Ain Shams center for organ transplantation
AST	**:**	Aspartate aminotransferase
ASUSH	**:**	Ain Shams University Specialized Hospital
ATG	**:**	Anti-thymocyte globulins
B cell	**:**	B lymphocyte
BMI	**:**	Body mass index
C4	**:**	Complement component 4
CBC	**:**	Complete blood count
CD	**:**	Cluster of differentiation
CI	**:**	Confidence interval
CKD	**:**	Chronic kidney disease
CLT	**:**	Cadaveric liver transplantation
CMV	**:**	Cytomegalo virus
CNI	**:**	Calcineurin inhibitor
CR	**:**	Chronic rejection
CsA	**:**	Cyclosporine A
CT	**:**	Computed tomography
CTP	**:**	Child-Turcott-Pugh score
DAA	**:**	Directly acting anti-viral
DCV	**:**	Daclatasvir
DDI	**:**	Drug-drug interactions
DDLT	**:**	Deceased donor liver transplantation
DM	**:**	Diabetes mellitus
DNA	**:**	Deoxy ribo nucleic acid
EASL	**:**	European association for the study of the liver
EBR	**:**	Elbasvir
EBV	**:**	Epstein Barr virus

EDHS	**:**	Egypt demographic and health survey
eGFR	**:**	Estimated glomerular filtration rate
EHIS	**:**	Egyptian Health Issues Survey
EHM	**:**	Extrahepatic manifestation
ELISA	**:**	Enzyme linked immunosorbent assay
ELITA	**:**	European liver and intestine transplant association
EOT	**:**	End of treatment
ERCP	**:**	Endoscopic retrograde cholangiopancreatography
ESLD	**:**	End stage liver disease
F	**:**	Fibrosis stage of liver tissue
FCH	**:**	Fibrosing cholestatic hepatitis
FDA	**:**	Food and drug administration
Fig.	**:**	Figure
GFR	**:**	Glomerular filtration rate
GGT	**:**	Glutamyl gamma transferase
GLE	**:**	Glecaprevir
GN	**:**	Glomerulonephritis
GRWR	**:**	Graft recipient weight ratio
GZR	**:**	Grazoprevir
HAT	**:**	Hepatic artery thrombosis
HAV	**:**	Hepatitis Avirus
HBcAb	**:**	Hepatitis B core antibody
HBIG	**:**	Hepatitis B immunoglobulin
HBsAb	**:**	Hepatitis B surface antibody
HBsAg	**:**	Hepatitis B surface antigen
HBV	**:**	Hepatitis B virus
HCC	**:**	Hepatocellular carcinoma
HCV	**:**	Hepatitis C virus
HE	**:**	Hepatic encephalopathy
HEV	**:**	Hepatitis E virus
HIV	**:**	Human immunodeficiency virus
HLA	**:**	Human leucocyte antigen
HRS	**:**	Hepatorenal syndrome
HSV	**:**	Herpes simplex virus
HTN	**:**	Hypertension
IDU	**:**	Injecting drug user
IFN	**:**	Interferon
IGD	**:**	Interferon induced graft dysfunction
IL	**:**	Interleukin
INR	**:**	International normalized ratio
IQR	**:**	Interquartile range
LDLT	**:**	Living donor liver transplantation

LDV	:	Ledipasvir
LFT	:	Liver function test
LT	:	Liver transplantation
MCS	:	Mixed cryoglobulinaemic syndrome
MELD	:	Model for end stage liver disease
MMF	:	Mycophenolate mofetil
mRECIST	:	Modified response evaluation criteria in solid tumors
MRSA	:	Methicillin resistant staphylococcus aureus
mTOR	:	Mammalian target of rapamycin
N	:	Number
NANBH	:	Non-A non-B hepatitis
NAS	:	Non- anastomotic stricture
NCCVH	:	National committee for control of viral hepatitis
NET	:	Neuroendocrine tumor
NHL	:	Non-Hodgkin lymphoma
NLI	:	National liver institute
NS	:	Not significant
NS3/4A	:	Non-structural protein complex 3/4A (serine protease; hepacivirin)
NS5A	:	Non-structural protein 5A (transcription activator)
NS5B	:	Non-structural protein 5B (RNA polymerase)
OLT	:	Orthotopic liver transplantation
OR	:	Odds ratio
P-glycoprotein	:	Permeability glycoprotein
PCR	:	Polymerase chain reaction
Peg-IFN	:	Pegylated interferon
PI	:	Protease inhibitor
PIB	:	Pibrentasvir
PPD	:	Purified protein derivative
PSA	:	Prostatic specific sntigen
PTLD	:	Post-transplant lymphoproliferative disease
PWID	:	People who inject drugs
RAS	:	Resistance associated substitutions
RBV	:	Ribavirin
REAL/WHO classification	:	Revised European American lymphoma/ World health organization classification
rHCV	:	Recurrent hepatitis C virus
RNA	:	Ribonucleic acid
RPR	:	Rapid plasma reagent
S	:	Significant
SAE	:	Serious adverse event
SBP	:	Spontaneous bacterial peritonitis

SD	:	Standard deviation
SFSS	:	Small for size syndrome
Sig.	:	Significance
SMV	:	Simeprevir
SOF	:	Sofosbuvir
SVR	:	Sustained virological response
SVR12	:	Sustained virological response 12 weeks after the end of treatment
SVR24	:	Sustained virological response 24 weeks after the end of treatment
Tac	:	Tacrolimus
TACE	:	Trans-arterial chemoembolization
TGF	:	Transforming growth factor
UK	:	United Kingdom
UNOS	:	United network for organ sharing
US	:	United states
VEL	:	Velpatasvir
VRE	:	Vancomycin-resistant Enterococcus
VZV	:	Varicella zoster virus

List of Tables

List of Figures

ABSTRACT

Introduction: Liver transplantation is the only curative treatment for ESLD and HCC**.** Liver disease resulting from chronic HCV infection is the leading indication for liver transplantation. For patients with detectable HCV-RNA levels at the time of transplantation, postoperative recurrence of HCV infection was "immediate and universal." Recurrent HCV infection follows an aggressive course and re-transplantation frequently is associated with a poor outcome.

Aim of the work: To compare between different available regimens of DAAs (sofosbuvir/ daclatasvir and sofosbuvir / ledipasvir) regarding the efficacy and safety for treatment of compensated recurrent hepatitis C Virus infection after liver transplantation in Egyptian patients.

Patients and methods: This prospective study was conducted on recipients, who underwent living donor liver transplantation in Ain Shams Center for Organ Transplantation (ASCOT) at Ain Shams University Specialized Hospital (ASUSH), Cairo, Egypt between June, 2016 and May, 2017. Data of the recipients, who underwent living donor liver transplantation during the study period, were reviewed and the patients who fulfilled the inclusion criteria were enrolled into this study. The patients who fulfilled the inclusion criteria and received antiviral treatment were followed up monthly during their treatment and after finishing treatment for at least 3 months.

Results: Treatment of HCV recurrence in liver transplant recipients with SOF+DCV±RBV or SOF/LDV+RBV seems to confer high rates of SVR. There was no difference between both regimens regarding adverse events. Prolonged treatment of HCV recurrence after LDLT (24 weeks) was significantly associated with a higher SVR (P=0.035).

Conclusion: Adding RBV to antiviral regimens in the treatment of HCV recurrence in liver transplant recipients doesn't seem to add to the efficacy of DAAs. Adherence to prolonged course of antiviral treatment (24 weeks) when treating HCV recurrence post liver transplantation seems to be associated with higher rates of SVR than shorter course (12 weeks) with no increase in the incidence of adverse events or rejection episodes.

Keywords: Liver transplantation, HCV recurrence, DAAs.

INTRODUCTION

Liver transplantation (LT) is the only curative treatment for end- stage liver disease (ESLD) and hepatocellular carcinoma (HCC) ***(Freeman et al., 2008).***

Hepatitis C virus (HCV) is a major cause of chronic hepatitis and liver cirrhosis and has been recognized as a potent risk factor of carcinogenesis and/or recurrence of HCC ***(Shindoh et al., 2013).***

Mohlman and colleagues in ***2015*** stated that, the prevalence of the two major biomarkers of HCV (the anti-HCV antibodies and HCV RNA) seropositivity in Egypt is estimated at 14.7 % and 9.8 %, respectively, in the general population; but it is much higher among those over age 50 (> 35% for anti-HCV antibodies and > 25% for HCV RNA)**.**

Liver disease resulting from chronic HCV infection is the leading indication for liver transplantation in the United States, Europe and Japan. For patients with detectable HCV-RNA levels at the time of transplantation, postoperative recurrence of HCV infection was "immediate and universal." Recurrent HCV infection follows an aggressive course and retransplantation frequently is associated with a poor outcome ***(Curry et al., 2015).***

LT recipients with chronic HCV infection have a lower graft survival than patients with non-HCV

indications for transplantation (***Thuluvath et al., 2010***). Many of these graft losses are related to recurrent HCV disease ***(Terrault et al., 2014)***. Without appropriate antiviral therapy, 10% to 25% of patients develop cirrhosis within 5 years after transplantation ***(Velidedeoglu et al., 2004)***.

Antiviral therapy could be administered before transplantation or early post-transplantation to suppress viral replication and reduce the risk of recurrence. However, this strategy is limited by poor tolerance and drugs side effects ***(Bzowej et al., 2011)***. Frequently, antiviral therapy is initiated when HCV recurs to obtain viral eradication and/or reduce disease progression ***(Roche and Samuel, 2012).***

The previously recommended treatment for HCV infection was a combination therapy consisting of pegylated interferon (Peg-INF) alpha and ribavirin (RBV)***(Ghany et al., 2009)***.Interferon (IFN) based combination therapy was commonly administered to prevent the progression of hepatitis C after LT, but its efficacy in LT recipients was limited ***(Ueda et al., 2014)***.

The emerging novel antivirals should optimize the treatment options, especially for difficult-to-treat patients, such as those who are suffering from advanced liver diseases or other co-infections and who have poor response rates to current regimens ***(Qian et al., 2016).***