Effect of Hepatitis C Virus Treatment on Rejection Incidence and Severity in post-liver transplant Recepients

Thesis

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Zeinab Mohamed

List of Contents

List of Tables

List of Tables (Cont…)

List of Figures

List of Abbreviations

Abb.	Full term
A.U.H	*Ain Shams University Hospital*
A2ALL	*Adult to Adult Living Donor Liver Transplantation*
AASLD	*American Association for the Study of Liver Diseases*
AIDS	*Acquired immunodeficiency syndrome*
Ala	*Alanine*
ALT	*Alanine aminotransferase*
APN	*Alanine aminopeptidase N*
ASCOT	*Ain shams center of liver transplantation organ*
AST	*Aspartate aminotransferase*
AZA	*Azathioprine*
BCRP	*Breast cancer resistance protein*
BMI	*Body mass index*
CAD	*Coronary artery disease*
CD	*Cluster of differentiation 8*
CKD	*Chronic kidney disease*
CMV	*Cytomegalovirus*
CNI	*Calcineurin inhibitor drugs*
CR	*Chronic rejection*
CsA	*Cyclosporine*
CTP	Child-Pugh-Turcotte
DAAs	*Directly acting antiviral drugs*
DSV	*Dasabuvir*
EBR	*Elbasvir*
EBV	*Epstein-Barr virus*
eGFR	Estimated Glomerular Filtration Rate

List of Abbreviations (Cont…)

Abb.	Full term
ESRD	*End stage renal disease*
EVR	*Everolimus*
GGT	*Gamma-glutamyl transpeptidase*
GLE	*Glecaprevir*
GZR	*Grazoprevir*
HAV	*Hepatitis A virus*
HBV	*Hepatitis B virus*
HCC	*Hepatocellular carcinoma*
HCV	*Hepatitis c virus*
HDmiRs	*Hepatocyte derived microRNAs*
HHV-8	*Human herpes virus 8*
HIV	*Human immune deficiency virus*
HIV	*Human immune deficiency virus.*
HLA	*Human leukocyte antigen*
HPS	*Hepatopulmonary syndrome*
HR	*Heart Rate*
HSV	*Herpes simplex virus*
IFN	*Interferon*
IL2	*Interleukin-2*
IMPDH	*Inosine monophosphate dehydrogenase*
INR	*International normalized ratio*
LDV	*Ledipasvir*
LT	Liver transplantation
MELD	*Model for End-Stage Liver Disease*
miR	*microRNA*
MMF	*Mycophenolate mofetil*
mTOR	*Mammalian target of rapamycin*
NPIs	*Nucleoside polymerase inhibitors*

List of Abbreviations (Cont…)

Abb.	Full term
NS3/4A	*Non-structural proteins 3/4A*
OATP	*Organic anion transporting polypeptide*
OBV	*Ombitasvir*
OLT	*Orthotopic liver transplantation*
OVB/PTV/r+DSV	*Ombitasvir/ Paritaprevir/Ritonavir+ Dasabuvir*
P-gp	*P-glycoprotein*
PIB	*Pibrentasvir*
PPHTN	*Portopulmonary hypertension*
PTLD	*post-transplant lymphoproliferative disorders*
PTV	*Paritaprevir*
QoL	*Quality of life*
RAI	*Rejection activity index*
RASs	*Resistance associated substitutions*
RCTs	*Randomized controlled trials*
RRB	*Regional Review Board*
SD	*Standard Deviation*
SOF	*Sofosbuvir*
SPSS	*Statistical Package for the Social Sciences*
SRL	*Sirolimus*
SRTR	*Scientific Registry of Transplant Recipients*
SVR	*Sustained viral response*
Tac	*Tacrolimus*
ULN	*Upper limit of normal*
UNOS	*United Network for Organ Sharing*
VDRL	*Venereal disease research laboratory*
VEL	*Velpatasvir*
VOX	*Voxilaprevir*
VZV	*Varicella zoster virus*

Abstract:

Background and Aims: HCV is a worldwide cause of chronic liver disease, particularly in Egypt where the most prevalent is genotype 4. HCV-associated cirrhosis is the most common indication for orthotopic liver transplantation (OLT) among adults. HCV infection remains a problem after transplantation, and recurrent hepatic infection is the leading cause of graft failure. Little is known about the long-term effects of direct acting antiviral therapy in patients after liver transplantation. We examined the incidence and severity of liver transplantation rejection in patients treated for HCV, post liver transplantation, with DAAs relative to the incidence and severity of liver transplantation rejection in patients treated for HCV, post liver transplantation, with Interferon based therapy and patients who didn't receive any treatment for HCV after transplantation.
Methods: The study was conducted on 90 patients who had underwent liver transplantation between 2010 and 2017 at Ain Shams Center for Organ Transplantation (ASCOT) with a minimum follow up period of 6 months. Patients were divided into three groups: group I included 16 patients that didn't receive antiviral treatment after liver transplantation, group II included 20 patients that had received interferon based therapy after liver transplantation and group III included 54 patients that had received direct acting antivirals after liver transplantation.
Results: Amongst group I, 2 patients (12.5%) developed acute graft rejection while in group II 2 patients (10%) developed chronic graft rejection and in group III 6 patients (11.11%) developed chronic rejection. In group I, all the patients (100%) had developed rejection that was diagnosed within one year of liver transplantation. In group II, 2 patients (100%) developed chronic graft rejection which occurred after one year of liver transplantation, one of them was on treatment with peg interferon and the other had already completed treatment. In group III, 2 patients (40%) had developed chronic rejection within one year of transplantation, while 4 patients (60%) had developed chronic rejection after one year of transplantation. One patient (16.67%) had developed rejection on treatment while 5 patients (83.33%) had developed rejection after the end of treatment. **Conclusion:** It was found that the incidence of chronic rejection was more in patients that had received antiviral treatment after liver transplantation, however no difference was noted between DAAs and peg-interferon. Chronic rejection was found to be more common when treatment was given over one year after liver transplantation (6 cases) as compared to within the 1st year (2 cases). This may be related to the withdrawal of immunosuppression treatment after one year of transplantation and maintenance on monotherapy.

Keywords: Hcv treatment, liver transplantation, rejection

INTRODUCTION

Hepatitis C is a worldwide problem. The hepatitis C virus (HCV) is a major cause of both acute and chronic hepatitis. The World Health Organization (WHO) estimates about 71 million people globally have chronic hepatitis C, with approximately 399, 000 dying from this infection as primarily due to cirrhosis and hepatocellular carcinoma ***(World Health Organization, 2017).***

The prevalence of HCV infection varies throughout the world. For example, Egypt had the highest number of reported infections, largely attributed to the use of contaminated parenteral antischistosomal therapy. This led to a mean prevalence of 22% of HCV antibodies in persons living in Egypt ***(Frank et al., 2000).***

What is well known that there has been a spectrum of treatments to target the public health disaster represented by the hepatitis C problem in Egypt ranging from the use of PEGylated interferon to the recent use of direct acting antiviral drugs ***(Elgharably et al., 2016).***

The era of recent direct-acting antivirals (DAAs) provides possibility of reducing disease burden and eliminating this blood-borne virus as a public health concern ***(World Health Organization, 2017).***

World Health Organization has recently formulated the "Global Health Sector Strategy on Viral Hepatitis", although the Egyptian government following successful negotiations for 99% discounted DAA prices, it launched a national HCV treatment program aiming to treat over 250, 000 chronically infected individuals per year, with the goal of achieving a national chronic infection prevalence of <2% by 2025 ***(Kouyoumjian et al., 2018).***

Aim of the Study

The aim of this study is to study relation of Directly –acting antivirals (DAAs) with the occurrence of liver transplantation rejection.

Chapter 1
TREATMENT OF HCV INFECTION

The goal of therapy is to cure HCV infection in order to:

(i) Prevent the complications of HCV-related liver and extra-hepatic diseases, including hepatic necroinflammation, fibrosis, cirrhosis, decompensation of cirrhosis, HCC, severe extra-hepatic manifestations and death.

(ii) Improve quality of life and remove stigma.

(iii) Prevent onward transmission of HCV.

The endpoint of therapy is a "sustained" viral response (SVR), defined by undetectable HCV RNA in serum or plasma 12 weeks (SVR12) or 24 weeks (SVR24) after the end of therapy ***(Martinot et al., 2010).***

All patients with current HCV infection and a positive HCV RNA test result, should be evaluated by a practitioner with expertise in assessment of liver disease severity and HCV treatment. Subspecialty care and consultation are required for persons with HCV infection who have advanced fibrosis or cirrhosis (stage F3 or above on Metavir scale), including possible referral for consideration of liver transplantation. In the United States, only an estimated 13% to 18% of HCV-infected persons had received treatment ***(Holmberg et al., 2013).***