Recurrent Hepatitis C Virus Infection In Egyptian Patients Post-Liver Transplantation

Thesis

Submitted for Partial Fulfillment of

Master Degree in Tropical Medicine

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بسم الله الرحمن الرحيم
قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا
عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ
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Eman M. Hasaneen

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AZA	Azathioprine.
ADV	Adefovir dipivoxil.
AIH	Autoimmune Hepatitis.
ALT	Alanine aminotransferase.
APRI	AST to Platelets Ratio Index.
ARF	Acute renal failure.
AST	Aspartate aminotransferase.
AVH	Acute viral hepatitis.
CBC	Complete blood count.
CDC	Centers for Disease Control and Prevention.
CHC	Chronic Hepatitis C.
CLD	Chronic liver disease.
CMV	Cytomegalovirus.
CNIs	Calcineurin inhibitors.
CNS	Central nervous system.
CPM	Central Pontine myelinolysis.
CsA	Cyclosporine.

DAAs	Direct antiviral agents.
DDLT	Deceased donor liver transplantation
DNA	Deoxyribonucleic acid.
EBV	Epstein Barr Virus.
EIA	Enzyme immunoassay.
ESLD	End stage liver disease.
EPO	Erythropoietin.
ETV	Entecavir.
EVR	Early virologic response.
GTP	Guanosine triphosphate.
HBV	Hepatitis B virus.
HCC	Hepatocellular carcinoma.
HE	Hepatic Encephalopathy.
HIV	Human immunodeficiency virus.
HPV	Human Papilloma Virus.
HRS	Hepatic renal syndrome.
IFN-a	Interferon a.
IMPDH	Inosine monophosphate dehdrogenase.

INR	International normalized ratio.
LAM	Long term Lamivudine.
LT	Liver Transplantation.
MELD	Model of end stage liver disease.
MMF	Mycophenolate mofetil.
MPA	Mycophenlic acid.
OLT	Orthotopic liver transplantation.
PAT	Parenteral Antischistosomal therapy.
PBC	Primary Biliary Cirrhosis.
PCR	Polymerase chain reaction.
PEG-IFN	Pegylated interferon.
PIs	Polymerase inhibitors
PSC	Primary sclerosing cholangitis.
PTLD	Post transplant lymphoproliferative disease.
RMP	Ribavirin-5- monophosphate.
RNA	Ribonucleic acid.
RTP	Ribavirin-5-triphosphate.
RT-PCR	Real-Time polymerase chain reaction.

SVR	Sustained virologic response.
TAC	Tacrolimus.
TDF	Tenofovir.
TIPS	Transjugular intrahepatic portosystemic shunts.
WHO	World Health Organization.

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INTRODUCTION:

Hepatitis C virus (HCV) has been estimated by the World Health Organization (WHO) to infect 170 million patients worldwide, with the highest prevalence rate among Egyptians (14% - 18%; approximately 10-fold greater than in the United States and Europe) ***(Mohamed et al., 2005)***. Because of the very high prevalence rate of HCV in the general Egyptian population, it accounts for most chronic liver disease and HCC cases in Egypt ***(Hassan et al., 2001; Strickland et al., 2002)***.

Hepatitis C virus genotype 4 (HCV-4) is the most common variant of the hepatitis C virus (HCV) in the Middle East and Africa, particularly Egypt. This region has the highest prevalence of HCV worldwide, with more than 90% of infections due to genotype 4 ***(Kamal et al., 2008).***

HCV is the most frequent indication for *liver transplantation (LT)* in the United States and in Europe. With the anticipated increase in patients requiring LT for HCV related liver disease, development of effective strategies to

reduce graft failure due to HCV recurrence is essential ***(Schiano and Martin, 2006)***. Recurrence of HCV following *living donor liver transplantation (LDLT)* occurs in over 95 percent of patients (***Dickson et al., 1996)***

Previous studies looking at large numbers of patients with adequate long-term follow-up have confirmed that patients with HCV undergoing liver transplantation have increased morbidity and mortality and have lower 5 and 10 year survival rates when compared to patients undergoing liver transplantation for other etiologies of cirrhosis ***(Brown, 2005).***

However, recurrent hepatitis C virus infection will remain the most frequent form of recurrent disease in liver transplant programs in future ***(Schiano and Martin, 2006).*** HCV recurrence following LDLT in HCV-genotype 4 patients is not significantly different from its recurrence for other genotypes ***(Mudawi et al., 2009).***

Post-transplant antiviral therapy in those with evidence of recurrent disease is the mainstay of management. A combination of pegylated interferon and ribavirin is the treatment of choice, and sustained virologic response is achieved with 48 weeks of treatment in approximately 30% of treated patients. Attainment of early loss of hepatitis C virus

RNA is highly predictive of sustained virologic response. Histologic improvements are seen in responders. Survival is prolonged among those achieving a sustained virologic response ***(Terrault, 2008)***

Risk factors for severe recurrent HCV include advanced donor age, HCV genotype 1, high HCV RNA levels before and after transplant, early histological recurrence of HCV, concomitant cytomegalovirus infection, the use of T lymphocyte-depleting immunosuppressive agents such as OKT3, and treatment of presumed acute cellular rejection with pulse corticosteroids. Data are conflicting as to whether recipient age, warm or cold ischemia times, gender, HLA mismatch, ethnicity or pre-transplant severity of illness influence the rate of recurrent HCV and its severity ***(Brown, 2005).***

A number of repots have described accelerated fibrosis progression post-liver transplantation and this may in part be due to the age of the donor liver allograft ***(Berenguer et al., 2002).***

Also, postoperative patient and graft survival rates for HCV (genotype 4)-related cirrhosis are more or less comparable to *deceased-donor liver transplants (DDLT)* reported in the literature. Clinical HCV recurrence after *living*