Hepatitis C Virus Recurrence in patients underwent Living Donor Liver Transplantation: efficacy and safety of treatment with combined Sofosbuvir and Daclatasvir

Thesis

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بسم الله الرحمن الرحيم
وَأَنْزَلَ اللهُ عَلَيْكَ الْكِتَابَ
وَالْحِكْمَةَ وَعَلَّمَكَ مَا لَمْ تَكُنْ تَعْلَمُ
وَكَانَ فَضْلُ اللهِ عَلَيْكَ عَظِيمًا
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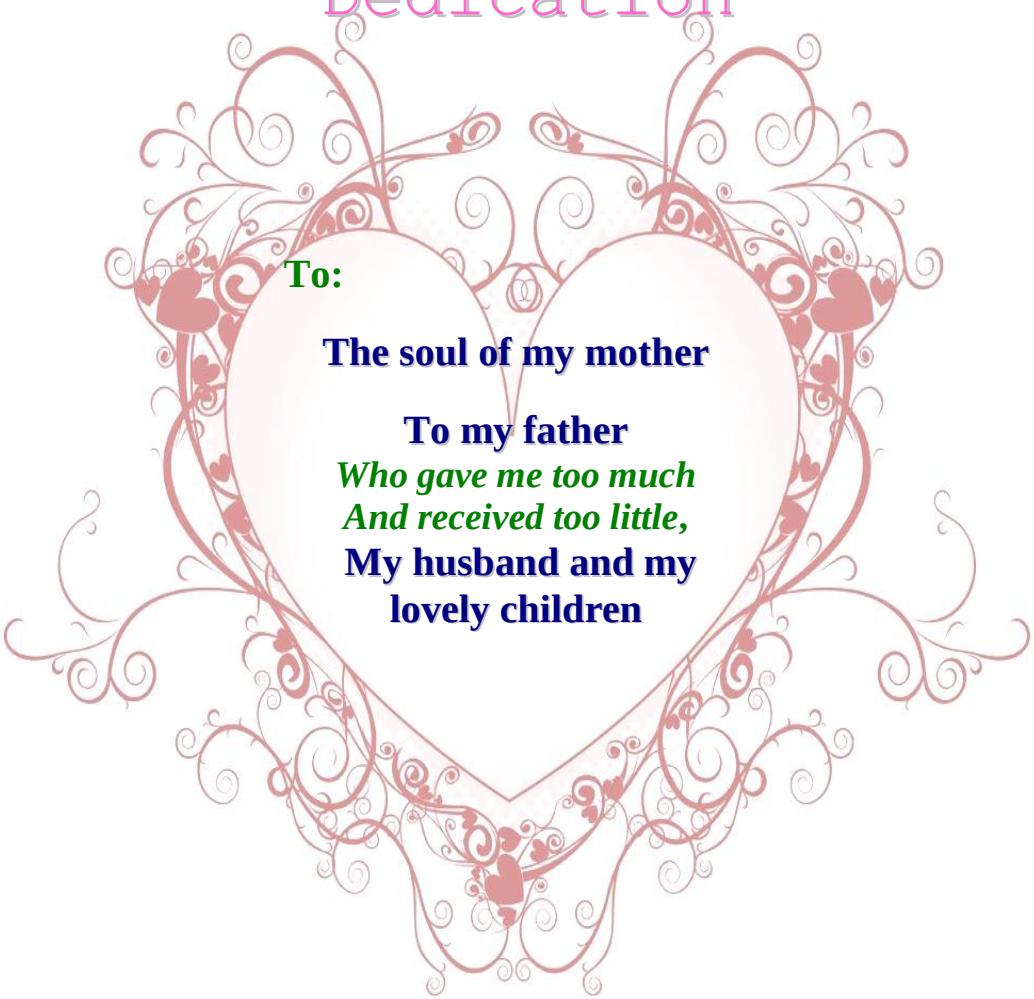
At last, I am indebted for my family

Eman Sabry

Dedication



To:

The soul of my mother

To my father
Who gave me too much
And received too little,
My husband and my lovely children

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List of Abbreviations

AASLD	American association for the study of liver disease
ACR	Acute Cellular Rejection
AFP	Alpha fetoprotein
ALT	Alanine amino transferase
AST	Aspartate amino trasnaminase
ATG	Antithymoglobulin
ASV	Asunaprevir
BMD	Bone mineral density
BOC	Boceprevir
CAD	Coronary artery disease
CIT	Cold Ischemia Time
CLD	Chronic Liver Disease
CMV	Cytomegallo virus
CNIs	Calcineurin Inhibitors
CT	Computed Tomograghy
CTP	Child-Turcotte-Pugh Score

CYP- 3A4	Cytochrome P 3A4
CYP 450	Cytochrome P 450
DAAs	Direct Acting Antivirals
DCV	Daclatasvir
DDLT	Deceased Donor Liver Trensplantation
EBV	Epstein Bar Virus
EDHS	Egypt Demographic and Health Survey
ELTR	European Liver Transplant Rigestry
ESLD	End Stage Liver Disease
GAG	Glycosaminoglycan
GFR	Glomerular filtration rate
GRWR	Graft recipient weight ratio
HALT-C	Hepatitis C antiviral long term treatment against cirrhosis
HBIG	Hepatitis B immunoglobulin
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus

HFL	Hepatic focal lesion
HIV	Human immunodeficiency virus
HLA	Human leucocyte antigen
HPS	Hepatopulmonary Syndrome
IL2	Interlukein 2
INR	International normalized ratio
IRES	Internal Ribosomal Entry Site
LDL	Low Density Lipoprotein
LDLT	Living Donor Liver Transplantation
LTx	Liver Transplantation
MELD	Model for end stage liver disease
MHC	Major histocompatibility complex
MMF	Mycophenol Mofetil
NIs	Nucleoside inhibitors
NODM	New onset diabetes mellitus
NTR	Non Translated Region
ORF	Open Reading Frame
PBC	Primary biliary cirrhosis

PCR	Polymerase Chain Reaction
PEG-INF	Pegylated Interferone
PELD	Pediatric End Stage Liver Disease
PIs	Protease inhibitors
PSC	Primary Sclerosing Cholangitis
PTLD	Post transplant lymphoproliferative disease
RBV	Ribavirin
RdRp	RNA dependant RNA polymerase
SD	Standard deviation
SOC	Standard of care
SOF	Sofosbuvir
SP	Signal Peptidase
SPP	Signal Peptide Peptidase
SVR	Sustained Virological Response
TIPS	Transjugular intrahepatic portosystemic shunts
TPV	Telaprevir
UNOS	United Network For organ Sharing
US	Ultrasound

UTR	Untranslated Region

ABSTRACT

Background: Treatment of hepatitis C in the post-liver transplantation patient is a rapidly evolving field. When treating hepatitis C in this setting, the main goals of therapy include: (a) cure of HCV chronic infection in the allograft post-transplant, (b) minimize the risk of developing HCV associated complications in the allograft, such as fibrosingcholestatic hepatitis and allograft failure, and (c) prevent development of hepatic fibrosis and thus preserve the function of the transplanted liver. The Association of sofosbuvir and daclatasvir has been shown to have very high antiviral efficacy when administered,with or without ribavirin,to previously naïve or non-responder patients with chronic HCV infection. Combination with daclatasvir in a LT recipient with severe recurrent cholestatic hepatitis C has been reported,showing a favourable outcome and the lack of drug interactions with calcineurin inhibitors (CNI).

Aim of the work: The purpose of this study was to evaluate the virological response,clinical efficacy and safety of the combined sofosbuvir and daclatasvir inliving donor liver transplant recipients with recurrent hepatitis Cfollowing transplantation and screening for the development ofhepatocellular carcinoma during ,after end of treatment or during followup.

Patients and Methods: This study included 40 patients underwent living donor liver transplantation during the period from January 2015 till December 2015 who started treatment at least 3 months following transplantation. Laboratory studies were done, IncludingCBC, liver function tests, liver enzymes,coagulation profile, sodium, potassium, kidney function tests, thyroid function tests, autoimmune markers (ANA, ASMA, LKM, AMA), HCV antibodies and quantitative HCV RNA by PCR, HBV markers, CMV antibodies, EBV antibodies and tumor markers including AFP ,CEA and CA19-9. Imaging studies including, abdominal ultrasonography, Doppler ultrasound, arteriography, venoportography, Fibroscan and Triphasic computed tomography with contrast.

Results:

Conclusion: Non interferon-based therapies with oral DAA agentshave revolutionized the treatment of HCV recurrencepost-transplant. These regimens have consistentlydemonstrated high SVR rates, shorter treatment courses,and a more favorable side effect profile than interferonbasedtherapies.Although DAA agents are effective even in advancedliver disease, SVR rates seem diminished when comparedwith patients with minimal liver disease. Further studies are needed to clarify whether DAAsincrease HCC incidence and to determine the naturalhistory and baseline post -SVR HCC incidence accordingto the type of ant i -HCV therapy in each specific patientpopulation.

Key words: Hepatitis C Virus, Recurrence, Living Donor Liver Transplantation, Sofosbuvir and Daclatasvir.