



**Study of IL28B gene variation as a  
predictor of response to Directly Acting  
antiviral therapy in Hepatic  
transplantation Hepatitis C Egyptian  
Patients**

*Thesis*

*Submitted for Partial Fulfillment of M.D  
Degree in internal medicine*

*By*

**Shady Samir AbdelHamid Ghait**  
*M.Sc Ain Shams University*

*Under supervision of*

**Prof Dr. Hanan Mahmoud Badawy**

*Prof. of Internal Medicine and Gastroenterology and Hepatology  
Faculty of Medicine-Ain Shams University*

**Dr. Sherif Sadeq Taha**

*Assistant Prof. of Internal Medicine and Gastroenterology and Hepatology  
Faculty of medicine-Ain Shams University*

**Dr. Yaser Omar Abdelrahman**

*Lecturer of Internal Medicine and Gastroenterology and Hepatology  
Faculty of Medicine-Ain Shams University*

**Dr. Shimaa Husein Gadallah**

*Lecturer of Internal Medicine and Gastroenterology and Hepatology  
Faculty of medicine-Ain Shams University*

*Faculty of Medicine  
Ain Shams University*

*2019*



دراسة الأختلاف الجينى للانترليوكين ٢٨-ب لتنبؤ  
الاستجابة للأدوية المباشرة المضادة لفيروس سى عن  
طريق الفم فى مرضى فيروس سى المصريين بعد  
زراعة الكبد

رسالة

توطئة للحصول على دكتوراه الباطنة العامة

مقدمة من

شادى سمير عبد الحميد غيط

ماجستير الباطنة العامة

جامعة عين شمس

تحت إشراف

أ.د. حنان محمود بدوى

أستاذ الباطنة العامة و الجهاز الهضمى و الكبد  
كلية الطب-جامعة عين شمس

د. شريف صادق طه

أستاذ مساعد الباطنة العامة و الجهاز الهضمى و الكبد  
كلية الطب-جامعة عين شمس

د. ياسر عمر عبد الرحمن

مدرس الباطنة العامة و الجهاز الهضمى و الكبد  
كلية الطب-جامعة عين شمس

د. شيماء حسين جاد الله

مدرس الباطنة العامة و الجهاز الهضمى و الكبد  
كلية الطب-جامعة عين شمس

كلية الطب

جامعة عين شمس

٢٠١

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

# قالوا

لَسْبَدَانِكَ لَا نَعْلَمُ لَنَا  
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ  
الْعَلِيمُ الْعَظِيمُ

صدق الله العظيم

سورة البقرة الآية: ٣٢

## Acknowledgment

*First, I would like to thank Allah a lot for Blessing this work until it has reached its end, as a part of his generous help throughout our life.*

*I would like to direct my special thanks to Prof. Dr. Hanan Mahmoud Badwy, Professor of Internal Medicine and Gastroenterology, Faculty of Medicine, Ain Shams University for his great support and advice, her valuable remarks that gave me the confidence and encouragement to fulfill this work.*

*I am really so grateful to Prof. Dr. Sherif Sadek Taha Professor of General Surgery, hepatobiliary and liver transplantation, Faculty of Medicine, Ain Shams University for being a constant source of encouragement throughout my study and giving me all his time to help me.*

*My profound thanks and deep appreciation to Prof. Dr. Yaser Omar Abdelrahman Professor of Internal Medicine and Gastroenterology, Faculty of Medicine, Ain Shams University for his valuable supervision and direction that extended throughout this work.*

*I am also thankful to Dr. Shaimaa Husein Gadallah Lecturer of Internal Medicine and Gastroenterology, Faculty of Medicine, Ain Shams University for being a constant source of encouragement throughout my study and giving me all her time to help me.*

*Really I can hardly find the words to express my gratitude to. Dr. Ramy Samir Ghait of Internal Medicine and Gastroenterology, Faculty of Medicine, Ain Shams University, for his invaluable help, fruitful advice, offered to me step by step till this work essay finished.*

*Last but not least, I dedicate this work to my family, whom without their sincere emotional support, pushing me forward this work would not have ever been completed. I owe you every achievement throughout my life.*

# List of Contents

Title	Page No.
List of Tables .....	6
List of Figures .....	9
List of Abbreviations .....	12
Introduction .....	1
Aim of the Work.....	4
Review of Literature	
▪ Living Donor Liver Transplantation .....	5
▪ Interleukin-28B .....	39
▪ The Effect of Interleukin 28B Gene Polymorphism on the Virological Response in Chronic HCV Infected Patients .....	52
Patients and Methods .....	63
Results .....	67
Discussion .....	92
Summary .....	99
Conclusion.....	102
Recommendations .....	103
References .....	104
Arabic Summary .....	—

# List of Tables

Table No.	Title	Page No.
Table (1):	Exceptions to MELD score.....	12
Table (2):	Histologic rejection activity index for liver transplants RAI <4 is referred to mild acute rejection, 4-6 is considered moderate, RAI>6 is considered severe.....	35
Table (3):	Comparison between different genotypes of IL28B of group 1 regarding baseline patients characteristics before transplantation.....	67
Table (4):	Comparison between different genotypes of IL28B of group 2 regarding baseline patients characteristics.....	69
Table (5):	Shows comparison between the two types of regimen (sof-led) and (sof-dac) regarding baseline patients characteristics in group 1.....	70
Table (6):	Shows comparison between the two types of regimen (sof-led) and (sof-dac) regarding baseline patients characteristics in group 2.....	72
Table (7):	Shows comparison between group 1 (transplanted) and group 2 (non transplanted) regarding baseline patients characteristics.....	73
Table (8):	Shows comparison between group 1 (transplanted) and group 2 (non transplanted) regarding IL28B genotype frequency.....	77
Table (9):	Shows comparison between group 1 (transplanted) and group 2 (non transplanted) regarding HCV end treatment response.....	78

## List of Tables Cont...

Table No.	Title	Page No.
Table (10):	Shows comparison between group 1 (transplanted) and group 2 (non transplanted) regarding HCV sustained virological response. ....	79
Table (11):	Shows comparison between results of (sof-led) regimen and (sof-dac) regimen of group 1 (cirrhotic transplanted) regarding end treatment response.....	80
Table (12):	Shows comparison between results of (sof-led) regimen and (sof-dac) regimen of group 1 (cirrhotic transplanted) regarding sustained virological response(SVR). ....	81
Table (13):	Shows comparison between results of (sof-led) regimen and (sof-dac) regimen of group 1 (cirrhotic transplanted) regarding IL28B genotype frequency.....	82
Table (14):	Shows comparison between results of (sof-led) regimen and (sof-dac) regimen of group 2 (cirrhotic) regarding end treatment response. ....	83
Table (15):	Shows comparison between results of (sof-led) regimen and (sof-dac) regimen of group 2 (cirrhotic) regarding sustained virological response.....	84
Table (16):	Shows comparison between results of (sof-led) regimen and (sof-dac) regimen of group 2 (cirrhotic) regarding IL28B genotype frequency.....	85
Table (17):	Shows end treatment response of HCV among different types of IL28B genotypes in group 1 (cirrhotic transplanted). ....	86

## List of Tables Cont...

Table No.	Title	Page No.
Table (18):	Shows sustained virological response of HCV among different types of IL28B genotypes in group 1 (cirrhotic transplanted). .....	87
Table (19):	Shows end treatment response of HCV among different types of IL28B genotypes in group 2 (cirrhotic). .....	88
Table (20):	Shows sustained virological response of HCV among different types of IL28B genotypes in group 2 (cirrhotic). .....	89
Table (21):	Shows overall IL28B genotype frequency in group 1.....	90
Table (22):	Shows the percentage of SVR according to the distribution of the genotypes of IL28B in both donors and recipients of group 1. ....	90



# List of Figures

Fig. No.	Title	Page No.
<b>Figure (1):</b>	Shows PT changes among different genotypes of IL28B of group 1.....	68
<b>Figure (2):</b>	Shows comparison between the two subgroups of group 1 regarding the age.....	71
<b>Figure (3):</b>	Shows comparison between group 1 and group 2 regarding the age. ....	74
<b>Figure (4):</b>	Shows comparison between group 1 and group 2 regarding the sex.....	74
<b>Figure (5):</b>	Shows comparison between group 1 and group 2 regarding the PT and MELD.....	75
<b>Figure (6):</b>	Shows comparison between group 1 and group 2 regarding the albumin, bilirubin and creatinine. ....	75
<b>Figure (7):</b>	Shows comparison between group 1 and group 2 regarding the type of regimen.....	76
<b>Figure (8):</b>	Shows comparison between group 1 (transplanted) and group 2 (non transplanted) regarding IL28B genotype frequency.....	77
<b>Figure (9):</b>	Shows comparison between group 1 (transplanted) and group 2 (non transplanted) regarding HCV end treatment response.....	78
<b>Figure (10):</b>	Shows comparison between group 1 (transplanted) and group 2 (non transplanted) regarding HCV sustained virological response. ....	79
<b>Figure (11):</b>	Shows comparison between results of (sof-led) regimen and (sof-dac) regimen of group 1 (cirrhotic transplanted) regarding end treatment response. ....	80

# List of Figures

Fig. No.	Title	Page No.
<b>Figure (12):</b>	Shows comparison between results of (sof-led) regimen and (sof-dac) regimen of group 1 (cirrhotic transplanted) regarding sustained virological response(SVR).....	81
<b>Figure (13):</b>	Shows comparison between results of (sof-led) regimen and (sof-dac) regimen of group 1 (cirrhotic transplanted) regarding IL28B genotype frequency. ....	82
<b>Figure (14):</b>	Shows comparison between results of (sof-led) regimen and (sof-dac) regimen of group 2 (cirrhotic) regarding end treatment response.....	83
<b>Figure (15):</b>	Shows comparison between results of (sof-led) regimen and (sof-dac) regimen of group 2 (cirrhotic) regarding sustained virological response. ....	84
<b>Figure (16):</b>	Shows comparison between results of (sof-led) regimen and (sof-dac) regimen of group 2 (cirrhotic) regarding IL28B genotype frequency. ....	85
<b>Figure (17):</b>	Shows end treatment response of HCV among different types of IL28B genotypes in group 1 (cirrhotic transplanted).....	86
<b>Figure (18):</b>	Shows end treatment response of HCV among different types of IL28B genotypes in group 1 (cirrhotic transplanted).....	87
<b>Figure (19):</b>	Shows end treatment response of HCV among different types of IL28B genotypes in group 2 (cirrhotic).....	88

# List of Figures

Fig. No.	Title	Page No.
<b>Figure (20):</b>	Shows sustained virological response of HCV among different types of IL28B genotypes in group 2 (cirrhotic). ....	89
<b>Figure (21):</b>	Shows the percentage of SVR according to the distribution of the genotypes of IL28B in both donors and recipients of group 1. ....	91

# List of Abbreviations

Abb.	Full term
AIDS.....	acquired immune deficiency response
AKI.....	Acute Kidney Injury
AR .....	Acute rejection
CKD .....	Chronic kidney disease
CMV.....	Cytomegalovirus
CNIs.....	Calcineurin inhibitors
DAAs.....	Direct acting antivirals
Dac.....	Daclatasvir
EBV.....	Epstein Barr virus infection
GWAS .....	Genome-wide association study
HA.....	Hepatic artery
HAS.....	Hepatic artery stenosis
HAT .....	Hepatic artery thrombosis
HBIG.....	HBV immunoglobulin
HCC .....	Hepatocellular carcinoma
HCV .....	Hepatitis C virus
IFN- $\lambda$ 3.....	Interferon lambda-3
IL28A.....	Interleukin 28A
IL28B.....	Interleukin 28B
INR .....	International normalized ratio
LDLT .....	Living Donor Liver Transplantation
Led .....	Ledipasvir
LT.....	Liver transplantation
MELD .....	Model for End Stage Liver Disease
NASH .....	Nonalcoholic steatohepatitis
NPV .....	Negative predictive value

## List of Abbreviations Cont...

Abb.	Full term
PBC.....	Primary Biliary Cirrhosis
PEI.....	Percutaneous ethanol ablation
PPV .....	Positive predictive value
PSC .....	Primary Sclerosing Cholangitis
PTA.....	Percutaneous transluminal angioplasty
PTLD .....	Post transplantation lymphoproliferative disease
PV .....	Portal vein
PVS .....	Portal vein stenosis
PVT .....	Portal vein thrombosis
RBV.....	Ribavirin
RFA.....	Radiofrequency ablation
RI .....	Resistance index
SAT .....	Systolic ascending time
SNP.....	Single nucleotide polymorphism
Sof.....	Sofosbuvir
SVR.....	Sustained virological response
TACE .....	Transarterial chemoembolization
UCSF.....	University of California, San Francisco criteria

## ABSTRACT

**Background:** IL28B gene polymorphisms are associated with the response to antiviral therapy in hepatitis C patients in the non-transplant setting.

**Objective:** To determine the prevalence and impact on clinical outcomes of donor and recipient IL28B genotypes among liver transplant recipients receiving directly acting antiviral therapy compared to those of HCV non-transplant patients.

**Patient and Methods:** This study included 60 patients divided into 2 groups: group 1 included 30 patients subjected to living donor liver transplantation and group 2 included 30 patients of HCV infection. Each group was subdivided into group A and group B according to the regimen of directly acting antiviral therapy (sofosbuvir-ledipasvir, sofosbuvir-daclatasvir). Liver transplantation was done between January 2016 and April 2018. Genotyping of the polymorphism was performed on DNA collected from all donors and recipients in group 1 before and after liver transplantation and also collected from all patients of group 2. Sustained virological response was found in 28 patients in group 1 (transplanted group) and 29 patients in group 2 (non-transplanted group) with no significant difference.

**Results:** No significant difference also was found in both groups according to the type of regimen. Also the type of genotype CC, CT and TT of IL28B in donors and recipients were not significantly associated or affecting the results of SVR in both groups of patients.

**Conclusion:** Our results support no role of recipient IL28B genotype in the response to directly acting antiviral drugs for hepatitis C recurrence. Interestingly, donor genotype seems not to influence the response pattern in recipients who have different IL28B genotype.

**Keywords:** IL28B: interleukin 28B, SVR: sustained virological response , sof : sofosbuvir , dac : daclatasvir , led : ledipasvir , HCV : hepatitis C virus.

## INTRODUCTION

**H**epatitis C virus (HCV) is an important etiology of chronic hepatitis and cirrhosis and is a leading indication for liver transplantation in adults around the world (*Ghani et al., 2009*).

HCV infection may lead to significant liver injury. Viral, environmental and host factors, including immunologic and genetic susceptibilities, may contribute to differences in the disease expression and treatment response. This genetic susceptibility has a significant part in developing of HCV infection, from viral antigen recognition and presentation to the type of immune response developed against the pathogen (*Promrat et al., 2003*).

The predictive factors of treatment response are also related to the virus and they can be classified as clinical, immunologic, and genetic factors (*Seeff and Hoofnagle, 2002*).

Gene polymorphisms that encode or regulate the host molecular expression may be useful as disease evaluation markers and therapy response predictors, moreover they could provide helpful information for understanding the complex mechanisms underlying the virus-host interaction and the variations observed in antiviral therapy responses (*Ge et al., 2009*).

The IL28B polymorphisms were considered the strongest baseline identified predictors of viral kinetics and spontaneous