



Ain Shams University
Faculty of Medicine
Internal Medicine Department

PERIPHERAL BLOOD T-CELL CD4 AND CD8 LEVELS IN SEROPOSITIVE HCV RENAL TRANSPLANTED PATIENTS

Thesis

*Submitted for the Partial Fulfillment of Master Degree in
Internal Medicine*

By

Mohamed Abd El Latif Mohamed

M.B.B.Ch.

Faculty of Medicine, Ain Shams University

Supervised by

Prof. Dr. Mohammed Ali Ibrahim

Head of Nephrology Department

Faculty of Medicine, Ain Shams University

Prof. Dr. Afaf Abd El alim Mostafa

Professor of clinical pathology

Faculty of Medicine, Ain Shams University

Dr. Dawlat Hussien Sany

Assistant Professor of Internal Medicine and Nephrology

Faculty of Medicine, Ain Shams University

**Faculty of Medicine
Ain Shams University**

2013

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالَ

سَبَّحَانَكَ لَا عِلْمَ لَنَا
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْعَظِيمُ

صدق الله العظيم

سورة البقرة الآية: ٣٢



Acknowledgement

*First of all I have to express my all thanks to **Allah** the most merciful the most helpful allowing me perform this work.*

*I would like to express my deepest gratitude and sincere appreciation to **Prof. Dr. Mohamed Ali Ibrahim**, Head of Nephrology Department, Faculty of Medicine, Ain Shams University for his continuous encouragement, his kind support and appreciated suggestions that guided me to accomplish this work.*

*I am also grateful to, **Prof. Dr. Afaf Abd El Alim Mostafa**, Professor of clinical pathology, Faculty of Medicine, Ain Shams University who freely gave her time, effort and experience along with continuous guidance through out this work.*

*Special thanks are extended to **Dr. Dawlat Hussien Sany**, Lecturer of Internal Medicine, Faculty of Medicine, Ain Shams University for her constant encouragement and advice whenever needed.*

*Finally, I would like to express my profound gratitude to **Dr. Ashraf Donia**, Head of Nephrology Department, National Institute of Urology and Nephrology his advice helped me in selection of cases and collection of data.*



Dedication

*To my Father; Mother;
and My Wife.*



Contents

Subjects	Page
• List of abbreviations	I
• List of Tables.....	IV
• List of Figures.....	V
• Introduction.....	1
• Aim of the work.....	4
• Review of literature	
- <i>Chapter I:</i> Hepatitis C Virus.....	5
- <i>Chapter II:</i> HCV And Renal Transplantation.....	19
- <i>Chapter III:</i> HCV And Immune System.....	51
• Patients & Methods.....	76
• Results.....	82
• Discussion.....	106
• Summary & Conclusion	116
• Recommendations.....	120
• References.....	121
• Arabic summary	

List of Abbreviations

ACE	Angiotensin converting enzyme
ACR	Acute cellular rejection
ALG	Antilymphoblast globulin
ALT	Alanine amino transferase
APC	Antigen-presenting cell
ARB	Angiotensin receptor (AT2) blockers
AT2	Angiotensin receptor
ATG	Antithymocyte globulins
AZA	Azathioprine
CCL3	Chemokine (C-C motif) ligand 3
CHC	Chronic hepatitis C
CNIs	Calcineurin inhibitors
CI	Confidence interval
CsA	Cyclosporine
CTL	Cytotoxic T Lymphocytes
CXCL8	Chemokine (C-X-C motif) ligand 8
CyA	Cyclosporin A
DC	Dendritic cells
DGF	Delayed graft function
DM	Diabetes mellitus
E	Envelope
ESRD	End stage renal disease
EIA	Enzyme immunoassay
ELISA	Enzyme-linked immunosorbent assay
FAE	Follicle-associated epithelium
FoxP3	Forkhead box p3
GM-CSF	Granulocyte/macrophage colony-stimulating faactor

GN	Glomerulonephritis
HCV	Hepatitis C virus
IFN	Intreferron
IFN-γ	Interferon-gamma
IRF3	Interferon regulatory transcription factor
IL-2	Interleukin-2
IL2RA	Interleukin 2 (IL2) receptor alpha
KDIGO	Kidney Disease Improving Global Outcomes
MMF	Mycophenolate mofetil
MN	Membranous nephropathy
MIP1α	Macrophage Inflammatory Protein- 1 alpha
MyD88	Myeloid differentiation primary response gene (88)
NS	Non structural proteins
MGN	Membranous GN
MHC	Major histocompatibility complex
MPGN	Membranoproliferative glomerulonephritis
mIg	Membrane immunoglobulin
NGF	Nerve growth factor
NKreg	Natural killer regulatory cells
NKT	Natural killer T
NODAT	New onset diabetes after transplantation
PDCs	plasmacytoid dendritic cells
PCR	Polymerase chain reaction
PEG-IFN	Pegylated interferon
PNALT	persistently normal alanine aminotransferase levels
PTDM	Post transplant diabetes mellitus
PTLD	Post-transplant lymphoproliferative disorder
RA	Rheumatoid arthritis
RER	Rough endoplasmic reticulum
RBV	Ribavirin

RNA	Ribonucleic acid
RR	Relative risk
RTRs	Renal transplant recipients
SDF-1	Stromal cell-derived factor
SRR	Steroid-resistant rejection
SVR	Sustained viral response
TAC	Tacrolimus
TAP1	Transporter associated with antigen processing 1
TCR	T cell receptor
Tc	T cytotoxic cells
TGFβ	Transforming growth factor β
Th	T helper cells
TBK1	TANK-binding kinase 1
TG	Transgenic
TNF-α	Tumor necrosis factor –alpha
Tr1	Type 1 regulatory T cells
Treg	T regulatory cells
USRDS	United States Renal Data System

List of Tables

Table No.	Title	Page
Table (1)	Summary of HCV related extrahepatic manifestations with clinical manifestations, differential diagnosis and treatment options.	11
Table (2)	Shows CD4 effector phenotypes	55
Table (3)	Comparison between the demographic characteristics in the studied groups.	83
Table (4)	Comparison between the studied groups regarding the immunological parameters.	84
Table (5)	Comparison between the studied groups regarding infection episodes needed hospital admission, infections treated in outpatient clinic & rate of infections/ month.	85
Table (6)	Comparison between the studied groups regarding blood chemistry.	86
Table (7)	Comparison between the group A and group B regarding the immunosuppression regimen.	87
Table (8)	Comparison between group A and group B regarding the number of acute rejection episodes.	88

Table No.	Title	Page
Table (9)	Correlations between infections needed hospital admission, infections treated in outpatient clinic and rate of infections/month with the immunological parameters and blood chemistry in HCV-ve recipients group.	89
Table (10)	Correlations between infections needed hospital admission, infections treated in outpatient clinic and rate of infections with the immunological parameters and blood chemistry in HCV +ve recipients group.	91
Table (11)	Correlation between infections needed hospital admission, infections treated in outpatient clinic and rate of infections/month with the immunological parameters and blood chemistry in all recipients.	93
Table (12)	Comparison between the demographic characteristics in the studied groups.	94
Table (13)	Comparison between the studied groups regarding blood chemistry.	96

Table No.	Title	Page
Table (14)	Comparison between group D and group E regarding infections needed hospital admission, infections treated in outpatient clinic & rate of infections/month.	97
Table (15)	Comparison between group D and group E regarding the number of acute rejection episodes.	98
Table (16)	Correlations between infections needed hospital admission, infections treated in outpatient clinic and rate of infection/month with age and blood chemistry in HCV-ve recipients.	99
Table (17)	Correlations between infections needed hospital admission, infections treated in outpatient clinic and rate of infection/month with age and blood chemistry in HCV+ve recipients.	101
Table (18)	Correlation between infections needed hospital admission, infections treated in outpatient clinic and rate of infection/month with blood chemistry in all recipients.	103

List of Figures

Figure No	Title	Page
Figure (1)	Hepatitis C virus (HCV): model structure and genome organization.	6
Figure (2)	Natural history of HCV Infecton.	8
Figure (3)	Algorithm for evaluation and management of chronic hepatitis c infection in patients who under consideration for kidney transplantation.	26
Figure (4)	Functions of TH1 and TH2 cells in immune response via the release of cytokines.	56
Figure (5)	The schema of innate immune suppression in chronic hepatitis c virus and the representative suppressive mechanisms.	65
Figure (6)	The schema of adaptive immune suppression in chronic hepatitis c and the representative suppressive mechanisms.	70
Figure (7)	Histogram represents the comparison between group A and group B regarding gender.	84
Figure (8)	Histogram represents the comparison between group A and group B regarding the immunosuppression regimen.	88

Figure No	Title	Page
Figure (9)	Histogram represents the comparison between group A and group B regarding the number of acute rejection episodes.	88
Figure (10)	Correlation between CD4 and infections. Treated in outpatient clinic in HCV +ve recipients (Group B).	92
Figure (11)	Histogram represents the comparison between group D and group E regarding gender.	95
Figure (12)	Histogram represents the comparison between group D and group E regarding the number of acute rejection episodes.	98
Figure (13)	Correlation between Age and infections treated in outpatient clinic in HCV-ve recipients (Group A)	100
Figure (14)	Correlation between urea and infections treated in outpatient clinic in HCV+ve recipients (Group D)	102
Figure (15)	Correlation between Age and infections treated in outpatient clinic in all renal allograft recipients (Group D and Group E).	104
Figure (16)	Correlation between urea and infections treated in outpatient clinic all renal allograft recipients (Group D and Group E).	105

Introduction

Renal transplantation offers the potential for improved quality and length of life to patients with end-stage renal disease (*Shapiro R, 2011*).

Renal transplant recipients represent an important group with high prevalence of HCV infection rates ranging from 10% to 50% (*Justa S et al., 2010*).

Infectious complications significantly increase morbidity and mortality after renal transplantation (*Sousa S et al., 2010*).

Approximately 80% of all renal transplant recipients have an infectious complication in the first year following transplantation (*Sousa S et al., 2010*).

In fact, in the past it was reported that patients with non-A non-B hepatitis had ‘a marked increase of life threatening extrahepatic complications’. This finding has been demonstrated in HCV-positive patients who had more frequent postoperative infections and potentially fatal infections of the central nervous system, lungs and blood stream (such as cytomegalovirus infection, tuberculosis, sepsis) (*Domi'nguez B and Morales JM, 2009*).

Although prior studies have shown an overall increased risk of death from infection in HCV-infected kidney transplant recipients. This study showed that the increased death rate from infection occurs in the early (6 months) post-transplant period. This raises as yet unanswered questions about the contribution of HCV infection to this increased mortality and suggests that one approach may be to modify the immunosuppression administered during this period (*Roth D et al., 2011*).

The presence of HCV infection in liver transplant recipients resulted in a significant increase in Regulatory T cells and a decrease in activated T cells in comparison with HCV-negative liver transplant recipients. These 2 findings indicate a potentially important effect of HCV on the immune system after transplantation through an increase in the suppressive role of Regulatory T cells and/or a decrease in activated T cells (*Ciuffreda D et al., 2010*).

CD4 T cell population was significantly increased in both HCV-negative and HCV-infected transplant recipients ($17.6 \pm 1.4\%$ and $0.5 \pm 0.9\%$, respectively) in comparison with healthy subjects and non transplanted HCV-infected patients. Interestingly, this activated CD4 T cell population was significantly lower in HCV-infected recipients versus HCV-negative recipients (*Ciuffreda D et al., 2010*).
