# Hepatitis C Virus Related Rheumatic Manifestations in a Cohort of Egyptian Patients with Chronic Hepatitis C before and after Direct-Acting Antiviral Therapy

#### **THESIS**

#### Submitted for partial fulfillment of MD Degree In Internal Medicine

 $\mathcal{B}y$ 

#### MAHMOUD MAHMOUD YOUSIF

M.B.B.CH, M.Sc

Under Supervision of

#### PROF.DR.ABDELAZEIM MOHAMMAD ELHEFNY

Lecturer of Internal Medicine, Rheumatology and Immunology
Faculty of Medicine, Ain Shams University

#### PROF.DR.REEM ABDELMONEIM HABEEB

Professor of Internal Medicine, Rheumatology and Immunology
Faculty of Medicine, Ain Shams University

#### DR.MARYAM AHMED ABDELRAHMAN

Lecturer of Internal Medicine, Rheumatology and Immunology
Faculty of Medicine, Ain Shams University

#### DR.RASHA NABIL THABIT

Lecturer of Internal Medicine, Rheumatology and Immunology
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
2019



# وقل اعملوا فسيرى الله عملوكم ورسوله والمؤمنون







سورة التوبة الآية (105)

#### Acknowledgement

First, thanks are all due to **ALLAH** for Blessing this work until it has reached its end, as a part of his generous help throughout our life.

I would like to express my deep gratitude and appreciation to PROF.DR.ABDELAZEIM MOHAMMAD ELHEFNY Professor Of internal Medicine, Rheumatology and Immunology, faculty Of Medicine, Ain Shams University.

I owe special feeling of gratitude to PROF.DR.REEM ABDELMONEIM HABEEB Professor of Internal Medicine, Rheumatology and Immunology, faculty Of Medicine, Ain Shams University for her encouragement, supervision, co-operation and help.

I feel greatly indebted to DR.MARYAM AHMED ABDELRAHMAN
Assistant Professor of Internal Medicine, Rheumatology and Immunology
Faculty of Medicine, Ain Shams University for her valuable criticism, generous
efforts and cooperation during all the stages of this work.

Words are not enough to express my deepest thank feeling and gratitude to DR.RASHA NABIL THABIT Lecturer of Internal Medicine, Rheumatology and Immunology Faculty of Medicine, Ain Shams University for her great help.

Finally I would like to thanks my parents, my wife and my daughters.

Mahmoud Mahmoud Yousif

### Contents

Title	Page
List of abbreviations	1
List of figures	IV
List of tables	VI
Introduction	1
Aim of the Work	5
Review of literature	
♣ I- Hepatitis C	6
<b>↓</b> II- Extrahepatic manifestations with chronic hepatitis C: Overview	51
♣ III- Rheumatic manifestations of chronic hepatitis C	87
Patients and Methods	124
Results	137
Discussion	165
Summary and conclusions	178
Recommendations	181
References	182
Arabic Summary	1

# List of tables

	ist of tables of review	Page
Table 1	Child-Pugh-Turcotte criteria	24
Table 2	A summary of the extrahepatic Manifestations of Hepatitis C	53
Table 3	Types of Cryoglobulinemia, Brouet reclassification	91
	List of tables of results	
Table 1	Demographics of the studied group.	139
Table 2	Incidence of base line HCV related rheumatic manifestations and autoantibodies frequency in the studied group.	139
Table 3	Hematological parameters in the studied group before and after treatment.	140
Table 4	Pre and post treatment values of Blood chemistry tests, PCR and urinary studies among the studied patients.	141
Table 5	Immunologic markers among all the studied patients before and after antiviral treatment.	

Table 6	Hematological parameters in pre and post treatment states among the studied patients with HCV related mixed cryoglobulinemia syndrome.	143
Table 7	Pre and post treatment values of Blood chemistry tests, PCR and urinary studies among the studied patients with HCV related mixed cryoglobulinemia syndrome.	144
Table 8	Comparison between pre and post treatment states as regards immunologic markers in patients with HCV mixed cryoglobulinemia syndrome	145
Table 9	Clinical response to antiviral treatment among patients with HCV related mixed cryoglobulinemia syndrome.	146
Table 10	Pre and post treatment values of haematological markers among the studied patients with HCV related arthralgia.	147
Table11	Pre and post treatment values of liver function tests and PCR among the studied patients with HCV related arthralgia.	147
Table 12	Pre and post treatment values of immunologic markers among the studied patients with HCV related arthralgia.	148

Table 13	Clinical response to antiviral treatment among patients with HCV related arthralgia.	149
Table 14	Pre and post treatment values of hematological markers among the studied patients with HCV related fibromyalgia	150
Table 15	Liver function tests and PCR before and after treatment in the studied patients with HCV related fibromyalgia	150
Table 16	Immunologic markers in pre and post treatment states among the studied patients with HCV related fibromyalgia	151
Table 17	Clinical response to treatment among the studied patients with HCV related fibromyalgia.	152
Table 18	Pre and post treatment values of all the measured variables among the studied patients with HCV related purpura.	153
Table 19	Hematological markers in virological responder patients before and after viral clearance.	154
Table 20	Pre and post treatment values of blood chemistry tests, PCR and urinary studies among the virological responder patients.	155

Table 21	Pre and post treatment values of immunologic markers in virological responder patients.	156
Table 22	Clinical response to treatment among virological responder patients.	157
Table 23	Pre and post treatment values of haematological markers among virological non responder patients.	159
Table 24	Pre and post treatment values of immunological markers among virological non responder patients.	160
Table 25	Pre and post treatment values of blood chemistry tests, PCR and urinary studies among the virological non responder patients.	161
Table 26	Clinical response to treatment among virological non responder patients.	162
Table 27	Comparison between responders and non responders regarding all measured variables after treatment.	163

# List of figures

	List of figures of review	Page
Figure 1	HCV genome	8
Figure 2	Schematic representation of the interactions between HCV and B cells	52
Figure 3	Role of B cell immunity in HCV- vasculitis	89
Figure 4	HCV-associated Cryovasculitis: Treatment options	98
Figure 5	Therapeutic strategies in HCV- Cryovasculitis	
Figure 6	Normal plain radiography of both painful hands in patient with HCVrA	
	List of figures of results	
Figure 1	Demographics of the studied group.	137
Figure 2	Distribution of rheumatic manifestations among the studied patients before treatment.	
Figure 3	Comparison between pre and post treatment states as regards Birmingham vasculitis activity score among the studied patients with HCV related MCS	146

Figure 4	Clinical response to treatment among patients with HCV related arthralgia.	149
Figure 5	Clinical response to treatment among the studied patients with mixed cryoglobulinemia syndrome who had achieved SVR12.	157
Figure 6	Clinical response to treatment among the studied patients with arthralgia who had achieved SVR12.	158
Figure 7	Clinical response to treatment among the studied patients with fibromyalgia who had achieved SVR12.	158

## List of abbreviations

Abbreviation	Acronym
AASLD-IDSA	American Association for the Study of Liver Diseases and the Infectious Diseases Society of America
AFP	Alpha feto protein
AIH	Autoimmune hepatitis
AIHA	Autoimmune haemolytic anaemia
AITP	Autoimmune thrombocytopenia
ALT	Alanine transaminase
ANA	Antinuclear antibody
Anti CCP	Anti citrulinated peptide
AST	Aspartate transaminase
BCLC	Barcelona clinic liver cancer
C3	Complement 3
C4	Complement 4
cANCA	Antineutrophil cytoplasmic antibodies
CBC	Complete blood picture
CGs	Cryoglobulins
CLD	Chronic liver disease
CTD	Connective tissue disease
DAAs	Direct acting antivirals
ds DNA	Double-stranded Deoxyribonucleic acid.
EASL	European Association for the Study of the Liver

ЕНМ	Extrahepatic manifestations
ELISA	Enzyme-linked immunosorbent assay
ERa	Early Rheumatoid arthritis
ESR	Erythrocyte sedimentation rate
FM	Fibromyalgia
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HCVrA	Hepatitis C virus related arthropathy
HIV	Human immune deficiency virus
INF	Interferon
LKMA	Liver kidney microsomal antibody
MC	Mixed cryoglobulinemia
MCS	Mixed cryoglobulinemia syndrome
NHL	Non-Hodgkin lymphoma
NOSA	Non organ specific auto- antibodies.
pANCA	Perinuclear Anti-Neutrophil Cytoplasmic Antibodies
PCR	Polymerase chain reaction.
Peg INF	Pegylated Interferon
RF	Rheumatoid factor
SS	Sjögren's syndrome
SSS	Symptom severity scale
SVR	Sustained virological response
TE	Transient elastography