Quantification of Core Antigen Monitors Efficacy of Combination Therapy of Sofosbuvir, Daclatasvir and Ribavirin in Egyptian Cirrhotic Patients with HCV Infection as an Alternative to PCR

Thesis

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List of Abbreviations

(g/l)……Gram per Litre

2'5'OAS ……..2'5'-Oligoadenylate Synthetase

AFP……. Alpha Feto Protein

ALT ……..….Alanine Aminotransferase

ALT ……Alanine Aminotransferase

APRI ……..Aspartate Aminotransferase to Platelet Ratio Index

ARFI ……..Acoustic Radiation Force Impulse

AST …….Aspartate Aminotransferase

BMI …….Body Mass Index

CDC ……Centers for Disease Control and Prevention

CHC ..... Chronic Hepatitis C

CLD……..…Chronic Liver Disease.

CLIA……Clinical Laboratory Improvement Amendments

CRP……. C Reactive Protein

CTGF ……..Connective Tissue Growth Factor

CTP ……Child-Turcotte-Pugh Classification System

CYP ……Cytochrome P450

DAAs …….Direct Antiviral Agents

DNA……... Deoxyribnucleic Acid

E proteins……...Envelope glycoproteins

EASL…….. European Assosciation for the Study of the Liver

EIA or ELIZA……Enzyme Linked Immunosorbent Assay

ER ……...Endoplasmic Reticulum

ESRD……..End Stage Renal Disease

ETR ……End of Treatment Response

EVR ……Early Virologic Response

FFP ……..Fresh Frozen Plasma

GE/mL…… Genome Equivalents per Milliliter

GFR…… Glomerular Filtration Rate

GGT…… γ Glutamyl Transferase

HA ……..Hyaluronic Acid

HA……Hyaluronic Acid

HAV……Hepatitis A Virus

HBV ……..Hepatitis B Virus

HBV……Hepatitis Bvirus

HCC ..... Hepatocellular Carcinoma

HCV Ab …….Hepatitis C Virus Antibody

HCV RNA……. Hepatitis C Virus Ribonucleic Acid

HCV ..... Hepatitis C Virus

HCV……Core Antigen (CAg)

HCV-Ag…….. Hepatitis C virus Antigen

HIV ..... Human Immunodeficiency Virus

HSC ……Hepatic Stellate Cells

HVR ……Hypervariable Regions

INR…….. International Normalized Ratio

IRES ……..Internal ribosome entry site

ISGF3……..IFN-Stimulated Gene Factor 3

ISGs ……IFN-Stimulated Genes

Jak/STAT……..…..Janus Kinase/Signal Transducers and Activators of Transcription

LDL…….Low Density Lipoprotein

LFTs ……Liver Function Tests

MC …….....Mixed Cryoglobulinemia

MFAP-4……...Microfibril-Associated Glycoprotein 4

mmol/l……. Millimoles per Litre

MRE ……Magnetic Resonance Elastography

NAAT …….Nucleic Acid Amplification Test

NAT ……Nucleic Acid Test

NCCVH ……..National Committee for Control of Viral Hepatitis

NCCVH……..National Committee for the Control of Viral Hepatitis

NPIs ……....Nucleoside Polymerase Inhibitors

NPV…….Negative Predictive Value

NSP…… Non Structural Proteins

OCI……..... Occult Hepatitis C Virus Infection

PBMCs ……Peripheral Blood Mononuclear Cells

PCR……Polymerase Chain Reaction

Peg IFN ……...Pegylated Interferon

PGA…….Prothrombin Index, Gamma Glutamyltransferaset, Apolipoprotein A1

P-gp …….P-glycoprotein

PICP ……Procollagen Type I Carboxy Terminal Peptide

PIIINP ……Procollagen Type III Amino-Terminal Peptide

PIs ……..Protease Inhibitors

PPV…….....Positive Predictive Value

PT…… Prothrombin Time

PTT……..Partial Thromboplastin Time

PWIDs……. People Who Inject Drugs

RBV ……Ribavirin

RdRp……..RNA Dependent RNA Polymerase

RIBA ……...Recombinant immunoblot assays

RT-PCR……. Real-Time Polymerase Chain Reaction

RT-PCR……. Reversr Transcription Polymerase Chain Reaction

RVR ……..Rapid Virological Response

SD…….Standard Deviation

SHEA ……..Society for Healthcare Epidemiology of America

SR-B1……..Scavenger Receptor Class B Type 1

SVR …….Sustained Virologic Response

TGF-β1……Transforming Growth Factor-β1

Th1……..T Helper 1 Cells

TIMP-1……Tissue Inhibitor of Metalloproteinases

TIMPs ……Tissue Inhibitors of Matrix Metalloproteinases

TMA ……Transcription-Mediated Amplification

TMDs ……..Two Transmembrane Domains

VCTE …….Vibration Controlled Transient Elastography

WHO …….. World Health Organization

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ABSTRACT

Background:. Hepatitis C virus (HCV) is a major public health problem throughout the world. Acute HCV infection is asymptomatic in most cases, and only 15% of cases are symptomatic,but Chronic hepatitis C (CHC) shows a variable clinical course, ranging from mild histopathological changes to active hepatitis and the development of hepatic fibrosis, cirrhosis and HCC. The aim of this work is to detect accuracy of core antigen in Egyptian cirrhotic patients with HCV Infection treated with combination therapy of Sofosbuvir, Daclatasvir and Ribavirin as an alternative to PCR.

Patients and methods: The study included20 Egyptian treatment-naïve chronic hepatitis C patients with cirrhosis (Cirrhosis was diagnosed on ultrasound basis) on Sofosbuvir ,Daclatasvir and Ribavirin. Results Treatment with sofosbuvir plus Daclatasvir and Ribavirin for 12 weeks resulted in undetectable HCV RNA by PCR in 95% (19/20) of the patients at the end of treatment and only 5% (1/20) of the patients achieved SVR after 6 months not 3(both HCV RNA AND HCV Core Antigen tests were negative for all patients).

Conclusion: In our study there was a correlation between HCV RNA and HCV core antigen results, so HCV core antigen can be used as an alternative marker to HCV RNA in treatment of HCV infected cirrhotic patients receiving Sofosbuvir, Daclatasvir and Ribavirin. during treatment and for monitoring its efficacy.

Key words: HCV, Acte HCV, HCV RNA, PCR, HCV Core Antigen, Chronic HCV.

Introduction

Hepatitis C virus (HCV) is a major public health problem throughout the world, **(Kazuaki et al., 2016).** Disease progression after HCV infection depends on several factors like gender, co infection with HIV, alcohol consumption, and duration of chronic infection **(Hajarizadeh, Grebely& Dore, 2013).**

Acute HCV infection is asymptomatic in most cases, and only 15% of cases are symptomatic with symptoms such as fatigue, nausea, joint pain or signs of liver damage (jaundice and increased liver enzymes). The majority of adults develop chronic infection (55–85%), with 15–45% resolving infection within the first six months. Chronic hepatitis C (CHC) shows a variable clinical course, ranging from mild histopathological changes to active hepatitis and the development of hepatic fibrosis, cirrhosis and HCC. **(Marc, et al., 2017)**

There are estimated to be at least 185 million HCV carriers worldwide, **(Kazuaki et al., 2016).** It has been reported that about 350,000 to 500,000 people die each year due to HCV related chronic liver disease such as liver cirrhosis or HCC **(WHO 2016).**

Hepatitis C viral infection is endemic in Egypt with the highest prevelance rate in the world (**Elgharably, et al., 2016)**

With the ultimate goal of achieving a more potent strategy to control transmission of HCV in Egypt, The Ministry of Health has set up 32 specialized centers for the nationwide therapy of HCV infection. The prevalence of HCV in adults decreases (7%) **(WHO, 2015).**

Screening for HCV antibody (HCV Ab) facilitates HCV surveillance in the

community **(Morisco etal., 2016).**

In the case of suspected acute hepatitis C or in immunocompromised patients, HCV RNA testing should be part of the initial evaluation. If anti_HCV antibodies are detected, HCV RNA should be determined by a sensitive molecular method. HCV core antigen is a surrogate marker of HCV replication and can be used instead of HCV RNA to diagnose acute or chronic infection when HCV RNA assays are not available or not affordable (core antigen assays are slightly less sensitive than HCV RNA assays for detection of viral replication) **(EASL Recommendations on Hepatitis C V irus treatment, 2016).**

New era for management of chronic HCV using direct antiviral agents (DAAs) started in 2013. DAAs are molecules that target specific nonstructural proteins of the virus and results in disruption of viral replication and infection. There are four classes of DAAs, all are nonstructural proteins 3/4A(NS3/4A) protease inhibitors (PIs) **(e.g. simeprevir, Paritaprevir, Grazoprevir)**, NS5B nucleoside polymerase inhibitors (NPIs) **(e.g. sofosbuvir)**, NS5B non-nucleoside polymerase inhibitors **(e.g. Dasabuvir)** and NS5A inhibitors **(e.g.**, **Daclatasvir, Ledipasvir, Ombitasvir, Elbasvir) (Poordad et al., 2012)**.

Testing for HCV core antigen presents a more attractive alternative owing to the lower cost and short turnaround time. HCV core antigen has been shown to be an indirect marker for HCV replication comparable to the detection of HCV RNA **(Florea et al., 2014).**