NON INVASIVE EVALUATION OF HEPATIC FIBROSIS IN PATIENTS WITH HEPATITIS C USING ELASTOGRAPHY

Thesis

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Abstract

HCV is a major cause of acute hepatitis and chronic liver disease, including cirrhosis and liver cancer. Globally, an estimated 170 million persons are chronically infected with HCV and 3 to 4 million persons are newly infected each year.

More than one million of people world wide die annually of hepatocellular carcinoma, the third highest cause of death due to malignant neoplasm. Hepatocellular carcinoma often develops as sequel of chronic viral hepatitis. It has been reported that the risk of hepatocellular carcinoma is related to the stage of hepatic fibrosis, making it a particularly important factor in the long term prognosis of chronic hepatitis C. The incidence of hepatocellular carcinoma increases along with progression of the stage.

The importance of histological diagnosis by liver biopsy for the assessment of the stage of hepatic fibrosis is widely acknowledged. However, due to its invasive nature, liver biopsy is limited when constant monitoring of the time course of changes in hepatic fibrosis is required, so non invasive tests may be more suitable in that context.

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LIST OF ABBREVIATIONS

Abbrev.	Meaning
+LR	Positive likelihood ratio
γ–GT	Gamma-glutamyl transpeptidase
µg	Microgram
2 hr PP	2 hours Post Prandial
AASLD	American Association for the Study of Liver Diseases
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMA	Antimitochondrial antibodies
APRI	AST Platelet Ratio Index
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUROC	Area Under the Receiver Operating Characteristic Curve
CA	California
Ca	California
CBC	Complete blood count
CD	Cluster designation
CDT	Carbohydrate Deficient Transferrin
CHC	Commonwealth Health Corporation
CI	Confidence interval
CIA	Chemiluminescence immunoassay
CLD	Chronic liver disease
CNS	Central Nervous System
CPT	Child-Pugh-Turcotte
CT	Computerized Tomography
CTP	Child-Turcotte-Pugh
D.Bil	Direct Bilirubinaemia
DANA	Dynamic Actor Network analysis
DDW	Digestive Diseases Week
dL	Decilitre
DNA	Deoxyribonucleic Acid
dsRNA	Double-stranded RNA
e.g.	for example
ECM	Extracellular matrix
EIA	Enzyme immunoassay
ELF	Enhanced Liver Fibrosis
ELISA	Enzyme-linked immunosorbent assay
et al	et alii = and others
ETR	End of treatment response
EVR	Early virologic response
F	Fibrosis
FBS	Fasting Blood Sugar
FDA	Food and Drug Administration
G-CSF	Granulocyte colony stimulating factor

LIST OF ABBREVIATIONS (Cont...)

Abbrev.	Meaning
GFR	Glomerular Filtration Rate
GGT	Gamma-glutamyl transpeptidase
h	Hours
HAART	Highly active antiretroviral therapy
HAI	Histology activity index
HAS	Haute Autorite´ de Sante´
HAV	Hepatitis A virus
HBcAb	Hepatitis B core Antibody
HBeAg	Hepatitis B envelope Antigen
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	The hepatitis C virus
HCV-LT	HCV liver transplant patients
HI-RTE	Hitachi Real-time Tissue Elastography
HIV	Human immunodeficiency virus
HS	Highly significant
i.e.	id est = that it
IASL	International Association for the Study of the Liver
IFN	Interferon
IFNα	Interferon Alpha
IFNγ	Type II interferon
IL	Interleukin
IMPDH	Inosine monophosphate dehydrogenase
INNO	Innogenetics
INR	International normalised ratio
iQur Ltd	UK pathology services in Southampton
IRES	Internal ribosome entry site
IRES	Internal ribosome entry site
ISIS	International School of Information Science
IU	International Unit
IU	International Units
KDIGO	Kidney Disease: Improving Global Outcomes
kg	Kilogram
kPa	Kilopascals
L	Liter
LB	Liver biopsy
LhRNAs	Long hairpin RNAs
LiPa	Line probe assay
LiPa	Chapter of HCV, P10
LKM	Liver Kidney Microsomal

LIST OF ABBREVIATIONS (Cont...)

Abbrev.	Meaning
-LR	Negative likelihood ratio
MELD	Model for End Stage Liver Disease
mEq	milliequivalent
mg	Milligram
miRNA	MicroRNA
MIU	Millie International Unit
mL	Milliliter
mm	Millimeter
MMPD	merimepodib
MR	Magnetic resonance
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic acid
NANB PTH	non-A, non-B post-transfusion hepatitis
NC	North Carolina
NC	North Carolina
NIH	National Institutes of Health
NJ	New Jersey
NM283	Valopicitabine also known as NM283 is a nucleosidepolymerase inhibitor.
NPV	Negative predictive value
NS	Non significant
NS protease	Nonstructural protease
NTR	Chap HCV, P54
NY	New York
P value	Predictive value
pANCA	Perinuclear Anti-Neutrophil Cytoplasmic Antibody
PC	Prothrombin Concentration
PCR	Polymerase chain reaction
PEG-IFN	Pegylated Interferon
PI	Protease inhibitor
PPV	Positive predictive value
PT	Prothrombin Time
RBCs	Red blood cells
RBV	Ribavirin
RIBA	Recombinant immunoblot assay
RNA	Ribonucleic acid
RNAi	RNA interference
ROC	Receiver-operating characteristics
ROI	Region of interest
RT	Real-Time
RVR	Rapid Virological Response

LIST OF ABBREVIATIONS (Cont...)

Abbrev.	Meaning
S	Significant
SD	Standard Deviation
SF	Significant fibrosis
SIA	Strip Immunoblot Assay
siRNA	Small interfering RNA
SLA antibodies	Soluble Liver Antibody
SOD	Superoxide dismutase
SP	Specificity
STAT	Specifically targeted antiviral therapy
STAT-C	Specifically targeted antiviral therapy drugs for HCV
SVR	Sustained virological response
SVR	Virological response rate
T.Bil	Total Bilirubinaemia
TE	Transient elastography
THV	Terminal Hepatic Vein
TIPS	Transjugular Intrahepatic Portosystemic Shunt
TLR	Toll-like receptor
TMA	Transcription-mediated amplification
TPV	Terminal Portal Vein
U.S.	United States
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
VX	Vertex Pharmaceuticals Telaprevir
X	The numerical average of a set of data is called **x**-bar

INTRODUCTION

HCV is a major cause of acute hepatitis and chronic liver disease, including cirrhosis and liver cancer. Globally, an estimated 170 million persons are chronically infected with HCV and 3 to 4 million persons are newly infected each year. HCV is spread primarily by direct contact with human blood. The major causes of HCV infection worldwide are use of unscreened blood transfusions, and re-use of needles and syringes that have not been adequately sterilized *(Chapman et al., 2006).*

More than one million of people world wide die annually of hepatocellular carcinoma, the third highest cause of death due to malignant neoplasm. Hepatocellular carcinoma often develops as sequel of chronic viral hepatitis. It has been reported that the risk of hepatocellular carcinoma is related to the stage of hepatic fibrosis, making it a particularly important factor in the long term prognosis of chronic hepatitis C. The incidence of hepatocellular carcinoma increases along with progression of the stage *(Shiratori et al., 2000).*

The importance of histological diagnosis by liver biopsy for the assessment of the stage of hepatic fibrosis is widely acknowledged. However, due to its invasive nature, liver biopsy is limited when constant monitoring of the time course of changes in hepatic fibrosis is required, and non invasive tests should be performed as well *(Ishak et al., 1995).*

Abdominal ultrasonography is the most useful non invasive diagnostic technique for the assessment of chronic hepatitis. However, for the assessment of staging in border line cases, ordinary ultrasonography is limited because images can change very slightly due to differences in the resolving power and image settings in the equipment used *(Fujimoto et al., 2008).*

Elastography uses the combined autocorrelation method to rapidly calculate the relative hardness of tissue from the degree of tissue distortion, and display this information as real-time, color images *(Fujimoto et al., 2008).*

The non invasive assessment was possible with Elastography, with the obtained liver elasticity score becoming significantly higher as the staging increased, satisfactorily reflecting the degree of fibrosis *(Fujimoto et al., 2008).*

AIM OF THE WORK

To investigate the usefulness of Elastography for the evaluation of hepatic fibrosis in patients with HCV, as an alternative modality to liver biopsy.