Changes in Serum Level of Autotaxin with Direct-Acting Antiviral Therapy in Patients with Chronic Hepatitis C as a Biomarker for Predicting Hepatic Fibrosis

Thesis

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List of Abbreviations

Abb.	Full term
aa	*Amino acid*
ADAMTS2	*A Disintegrin and Metalloproteinase with ThromboSpondin type*
apo	*Apolipoprotein*
apoB	*Apolipoprotein B*
apoE	*Apolipoprotein*
ATX	*Autotaxin*
BMI	*Body mass index*
CLDN1	*Claudin-1*
DAAs	*Direct-acting antivirals*
DALY	*Disability-adjusted life years*
DC-SIGN	*Dendritic cell-specific intercellular adhesion molecule 3 grabbing non integrin*
ECM	*Extracellular MATRIX*
EGF	*Epidermal growth factor*
Ennp…	*ecto-nucleotide pyrophosphatase/phosphodiesterase*
GAG	*Glycosaminoglycan*
GGT	*Glutamyltransferase*
GPAT	*Glycerophosphate acyltransferase*
HAI	*Histology activity index*
HCC	*Hepatocellular carcinoma*
HCV	*Hepatitis C virus*
HCV	*Hepatitis C virus*
HCVcc	*Cell culture-derived HCV*
HCV-LP	*HCV-like particles*
HCVpp	*HCV pseudoparticles*

List of Abbreviations cont...

Abb.	Full term
HDL	*High-density lipoprotein*
HIV	*Human immunodeficiency virus*
HVR-11	*Hypervariable region-1*
LDL	*Low-density lipoprotein*
LDLR	*LDL receptor*
LPA	*Lysophosphatidic acid*
L-SIGN	*DC-SIGNr, liver and lymph node specific*
Lyso PLD	*Lysophospholipase D*
MAGK	*Monoacylglycerol kinase*
MELD	*Model for End-Stage Liver Disease*
MMPs	*Matrix metalloproteinases*
MOH	*Egyptian Ministry of Health*
MSM	*Men who have sex with men*
NIs	*Nucleotide inhibitors*
NNIs	*Non-nucleotide inhibitors*
NOS2	*Nitric oxide synthase 2*
NOX	*NADPH oxidase*
NUC	*C-terminal nuclease-like*
PAI-1	*Plasminogen activator inhibitor 1*
PDE	*Phosphodiesterase*
PDGF	*Platelet-derived growth factor*
PegIFN	*Pegylated interferon*
PI3Ks	*Phosphoinositide 3-kinases*
ROS	*Reactive oxygen species*
siRNA	*Small interfering RNA*
SMB	*Somatomedin B-like*

List of Abbreviations cont...

Abb.	Full term
SR-BI	*Scavenger receptor class B type I*
SVR	*Sustained virological response*
TE	*Transient elastography*
TGF-beta-1	*Transforming growth factor beta-1*
TIMPS	*Metalloproteinases*
UPA	*Uroplasminogen activator*
VEGF	*Vascular endothelial growth factor*
VLDL	*Very low-density lipoprotein*
WHO	*World Health Organization*
YLD	*Years of life lost due to disability*
YLL	*Years of life lost due to premature death*

INTRODUCTION

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease, Worldwide it is estimated that 185 million people are chronically infected with Hepatitis C virus (HCV), with 3-4 million new infections per year and over 350,000 deaths due to HCV-related liver disease each year ***(Gower et al., 2016)***.

The impact of HCV infection is highly variable, ranging from minimal effects to chronic hepatitis, advanced fibrosis, cirrhosis, decompensated cirrhosis and hepatocellular carcinoma. Chronic HCV infection may induce also severe extra-hepatic complications ***(Maasoumy and Wedemeyer, 2016).***

The primary goal of HCV therapy is to cure the infection, i.e. to achieve a sustained virological response (SVR) defined as undetectable HCV RNA 12 weeks (SVR12) or 24 weeks (SVR24) after treatment completion. An SVR corresponds to a cure of the HCV infection, with a very low chance of late relapse ***(Bruno et al., 2016).***

An SVR is generally associated with normalization of liver enzymes and improvement or disappearance of liver necro-inflammation and fibrosis in patients without cirrhosis. Patients with advanced fibrosis (METAVIR score F3) or cirrhosis (F4) remain at risk of life-threatening complications. However, hepatic fibro-sis may regress and the risk of

complications such as hepatic failure and portal hypertension is reduced after an SVR ***(Nahon et al., 2017).***

Direct-acting antivirals (DAAs), the new interferon-free therapy, have been revolutionary in the treatment of hepatitis C. Previously, the disease was treated with pegylated interferon (PegIFN) combined with ribavirin. Direct-acting antivirals comprise four groups of medical substances which are mixed together (also with ribavirin) depending on the genotype of the hepatitis C virus and accompanying liver cirrhosis or other diseases. The groups are:

1. NS3/4A protease inhibitors – glecaprevir, paritaprevir, voxilaprevir, grazoprevir,
2. Nucleoside and nucleotide NS5B polymerase inhibitors – sofosbuvir,
3. NS5A inhibitors – ombitasvir, pibrentasvir, daclatasvir, elbasvir, ledipasvir, velpatasvir,
4. Non-nucleoside NS5B polymerase inhibitors – dasabuvir.

Invasive and noninvasive methods are used to monitor liver fibrosis. Invasive liver biopsies are difficult to undertake regularly because of the risk of bleeding, the length of hospitalization required to manage these risks, and the associated costs. Transient elastography (TE) and blood

sampling to determine the fibrosis marker levels are less-invasive liver fibrosis monitoring methods ***(Wang et al., 2009).***

Autotaxin (ATX) is a secreted enzyme originally discovered in conditioned medium from A2058 human melanoma cell cultures.ATX has an important enzymatic function in converting lysophosphatidylcholine to lysophosphatidic acid (LPA), which has various physiological roles. LPA also stimulates the proliferation and contractility of hepatic stellate cells. ATX is present in serum and is metabolized by liver sinusoidal endothelial cells ***(Reynaert et al., 2002).***

Liver fibrosis reduces the capacity to metabolize ATX, resulting in increases in the ATX level in serum. ATX has been shown to be useful as a serum marker for determining the fibrosis stage in CHC patients. In addition, ATX is suggested to be useful as an indicator of the severity of liver disease and for determining the prognosis of cirrhotic patients and HCC recurrence in combination with the levels of LPA receptors ***(Enooku et al., 2016).***