EFFECT OF LOSARTAN TREATMENT ON LIVER FIBROSIS OF CHRONIC HCV PATIENTS

Thesis

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By

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تـأثـــيرعقار" اللوسارتان" علـى تليف الكبد فـــي مرضى الالتهاب الفيروسي "ج"المزمن

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Shereif Morsy

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LIST OF ABBREVIATIONS

α-2-M	α -2-Macroglobulin
ACE	Angiotensin converting enzyme
ALT	Alanine transaminase
AMA	Antimitochondrial antibodies
ANG I	Angiotensin 1
ANG II	Angiotensin 2
AP	Abdominal paracentesis
AP-1	Activating protein type-1
APRI	AST-platelet ratio index
ARBs	Angiotensin receptor blockers
AST	Aspartate transaminase
AT	Angiotensin
AT1R	Angiotensin 1 receptor
AT2R	Angiotensin 2 receptor
BSL	Blood sugar level
CNS	Central nervous system
CTGF	Connective tissue growth factor
DM	Diabetes Mellitus
ECM	Extracellular matrix
ETA	Endothelin A
ETOH	Alcohol
FI	Fibrosis index
γGT	γ-glutamyl transpeptidase
GFR	Glomerular filtration rate
GH	Growth hormone
GHA	Growth hormone antagonist
GHR	Growth hormone receptor
GHRH	Growth hormone releasing hormone
HA	Hyaluronic acid
HAI	Histological activity index
HARI	Hepatic artery resistive index
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HGF	Hepatocyte growth factor
HRS	Hepatorenal syrdrome
HVPG	Hepatic venous pressure gradient
IFN	Interferon
IGF-1	Insulin-like growth factor-1
IGF-2	Insulin-like growth factor-2
IGFBPs	Insulin-like growth factors binding proteins
IGFs	Insulin-like growth factors

iNOS	Inducible nitric oxide synthase
kPa	KiloPascals
LDL	Low density lipoprotein
LDN	Lactate dehydrogenase
LVP	large volume paracentesis
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte chemotactin protein 1
MC-R	Mineralocorticoid receptor
MMPs	Matrix metalloproteinases
MTX	Methotrexate
NASH	Nonalcoholic steatohepatitis
NF-κB	Nuclear factor κB
NO	Nitric oxide
NSAIDS	Non steroidal anti-inflammatory drugs
PI3k	Phosphoinositol 3 kinase
PAI-1	Plasminogen activator inhibitor type 1
PBC	Primary biliary cirrhosis
PKC	Protein kinase C
PDGF	Platelet derived growth factor
PGs	Prostaglandins
PRA	Plasma renin activity
PPAR	Peroxisomal proliferator activated receptor
PRL	Prolactin
PTH	Parathyroid hormone
PVPV	Portal vein peak velocity
RAAS	Renin-angiotensin-aldosterone system
RBCs	Red blood cells
RBF	Renal blood flow
SHBG	Sex hormone binding globulin
siRNA	Small interfering RNA strands
SNS	Sympathetic nervous system
SRIF	Somatotropin release-inhibiting factor
T3	Triiodothyronine
T4	Thyroxine
TBG	Thyroxine-binding globulin
TIMP-1	Tissue inhibitor of metalloproteinases type 1
TGF-β1	Tumour growth factor-β1
TIMPs	Tissue inhibitors of matrix metalloprteinases
TLR4	Toll-like receptor 4
TNF-α	Tumour necrosis factor
TSH	Thyroid stimulating hormone
VEGF	Vascular endothelial growth factor
WBCs	White blood cells

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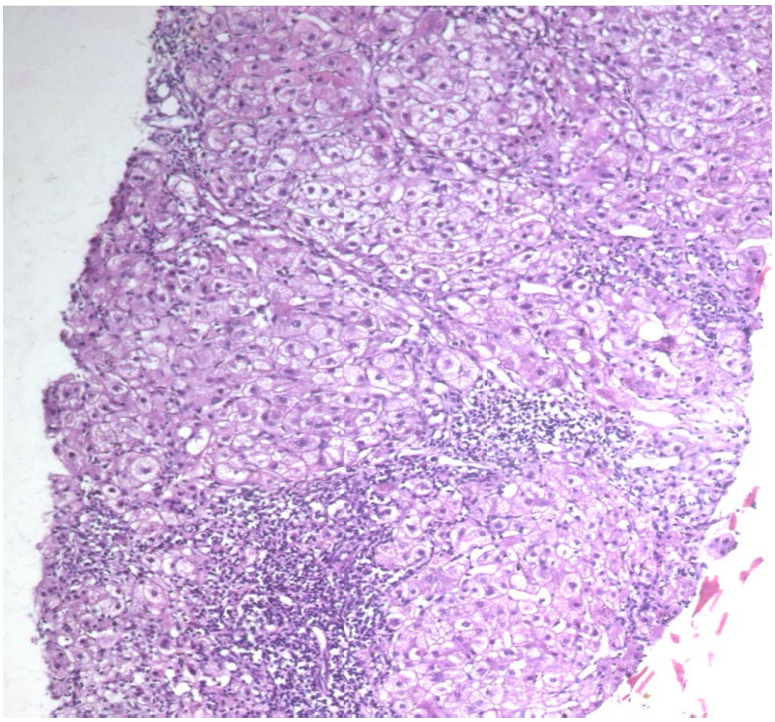
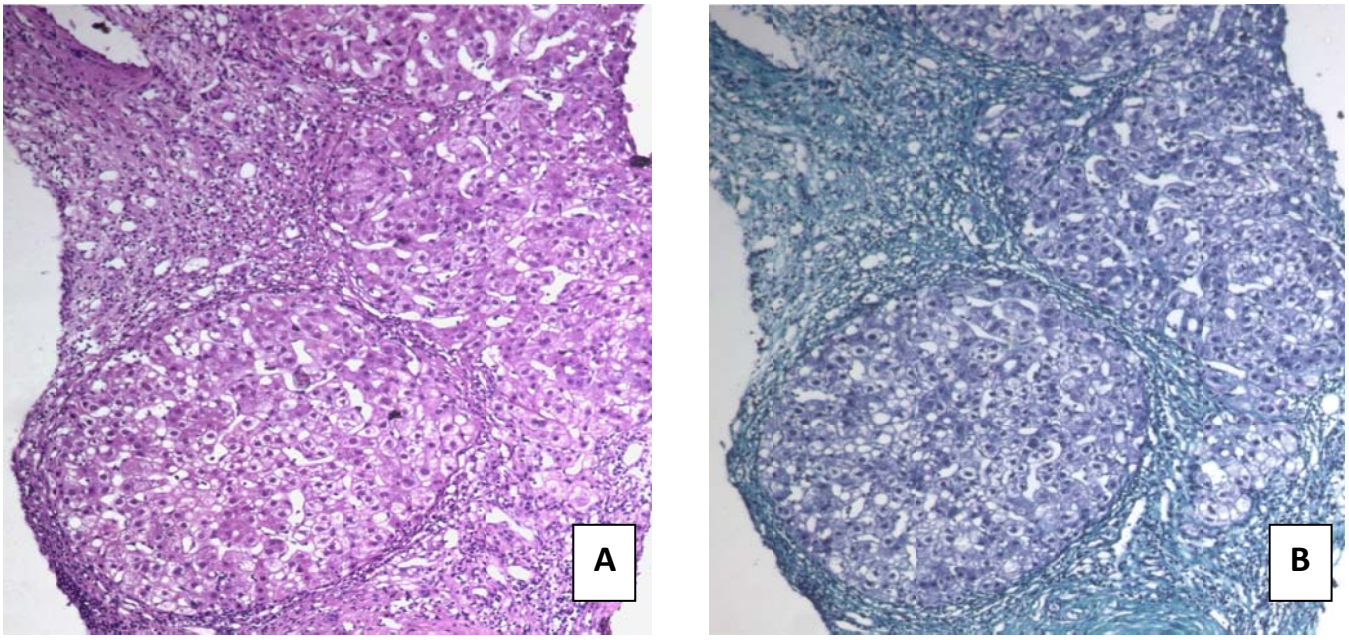


Slide.1 : Liver sections from a case of chronic HCV A2 F2 showing a portal tract extended with mild number of chronic inflammatory cells and fibrous tissue (H & E, X100).



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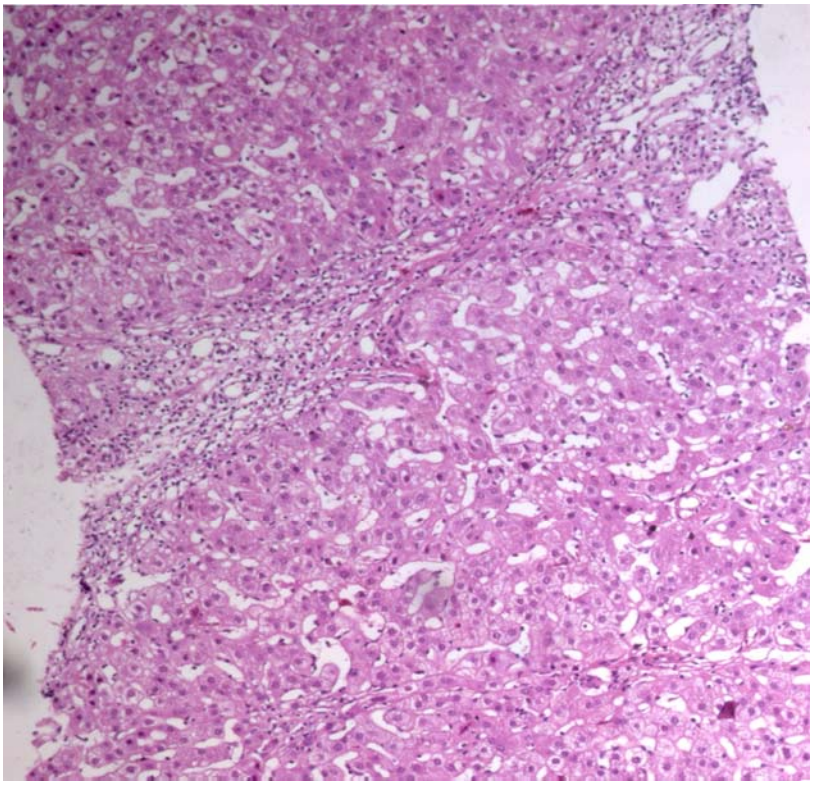

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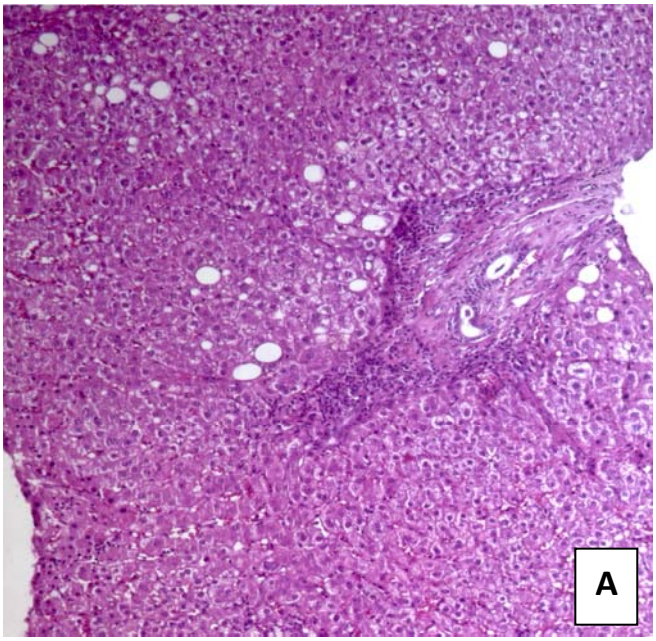

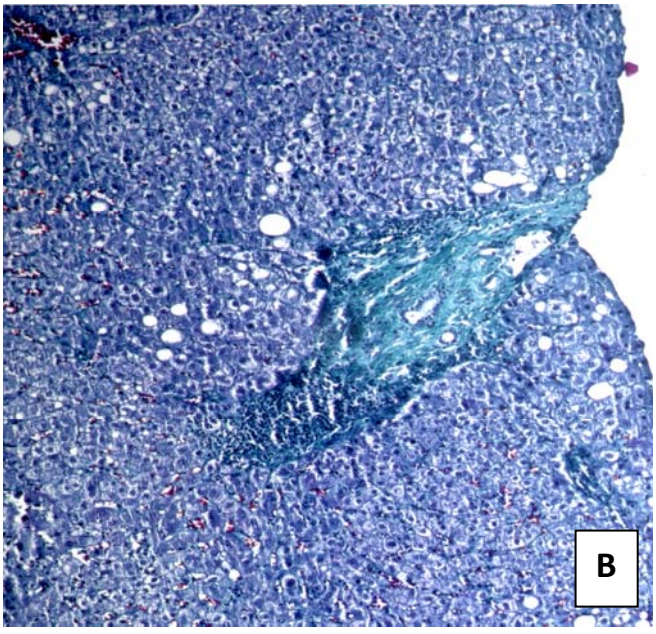

Slide.4 :A) Liver sections from a case of chronic HCV A1 F2 showing a portal tract extended with moderate number of chronic inflammatory cells and fibrous tissue(after treatment) (H & E, X100).B)same case stained with Masson Trichrome stain(X100)

Introduction and Aim of Work

The discovery of the hepatitis C genome in 1989 has led to the realization that this virus is a major worldwide health problem *(Alter et al, 1999)*. The hepatitis C virus (HCV) is one of the most common causes of chronic liver disease and a leading indication for liver transplantation. There are 170 million individuals infected worldwide. Approximately 20% of these individuals will progress to develop cirrhosis over the following 20 years. Death occurs at a rate of 2% to 5% per year once the patient develops cirrhosis and the risk of developing hepatocellular carcinoma (HCC) is 3% to 7% per year after the development of cirrhosis. Overall, 35% to 40% of all liver transplants performed in the US and Europe are performed for HCV *(National Institute of health (NIH), 2002; Shebab et al, 2002)*.

The national prevalence rate of HCV antibody positivity has been estimated to be between 10-13% (*Mohamed ,2004).*

Currently, individuals aged 40-59 years have the highest prevalence of hepatitis C infection. Healthcare costs for HCV include managing patients' symptoms, managing other organ involvement, treating HCV with antiviral agents, and managing end-stage liver disease as well as the cost of liver transplantation *(Wong et al , 2000).*

Although major progress has been made in the treatment of chronic HCV infection, the current treatment regimens, including Peginterferons in combination with Ribavirin, appear capable of eradicating HCV in only 30-50% of the treated patients *(NIH 2002)*. In this scenario, alternative medical strategies to reduce hepatic fibrosis are under investigation, since drugs with antifibrotic effects may be an option in the

treatment of patients with chronic hepatitis C who do not respond to the standard antiviral therapy *(Sookoian et al,2005).*

Much evidence suggests that hepatic stellate cells (HSCs) play important roles in the pathogenesis of liver fibrosis, since they were shown to undergo a transformation during the injury that is termed as activation. Furthermore, *in vitro* studies have shown that angiotensin II (ANGII) is a mitogenic protein for a number of cell types and between them are the HSCs . In these cells, ANGII upregulates the transforming growth factor beta 1 expression *via* AT-II type 1 receptor (AT1R) *in vitro (Bataller et al, 2003).*

Additionally, proliferation of activated HSCs was found in chronic liver diseases taking part in the development of liver fibrosis *(Yoshiji et al, 2001).* The fact that the actions of ANGII are mediated through AT1R is related to the therapeutic interventions, since AT1R can be completely blocked by losartan, a specific ANGII receptor antagonist. For instance, ANGII stimulated mRNA expression of TGF-beta and fibronectin can be reversed by saralasin and losartan, a nonselective and specific antagonists for AT1R receptors, respectively *(Leung et al,2004).*

Lastly, in animal models of fibrosis, chronic administration of losartan prevented the development of hepatic fibrosis and portal hypertension *(Croquet et al, 2002 and Yoshiji et al, 2005).*