

EFFECT OF LOSARTAN TREATMENT ON LIVER FIBROSIS OF CHRONIC HCV PATIENTS

Thesis

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of M.D. Degree in Tropical Medicine**

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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 |
| γ GT | 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 syndrome |
| 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- κ B | Nuclear factor κ B |
| 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- β 1 | Tumour growth factor- β 1 |
| TIMPs | Tissue inhibitors of matrix metalloproteinases |
| 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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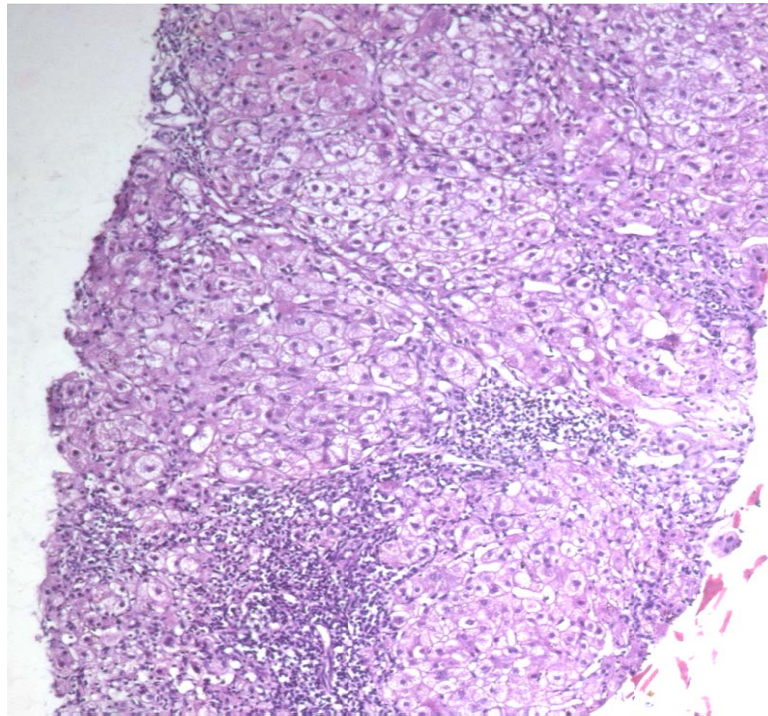
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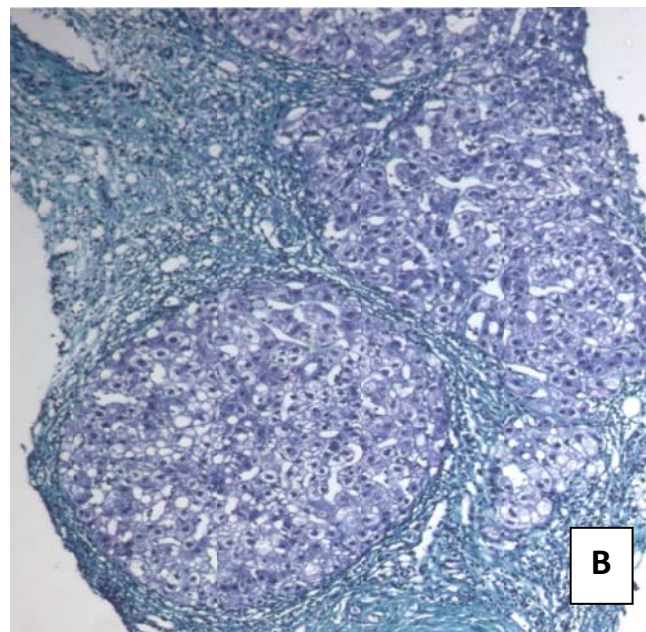
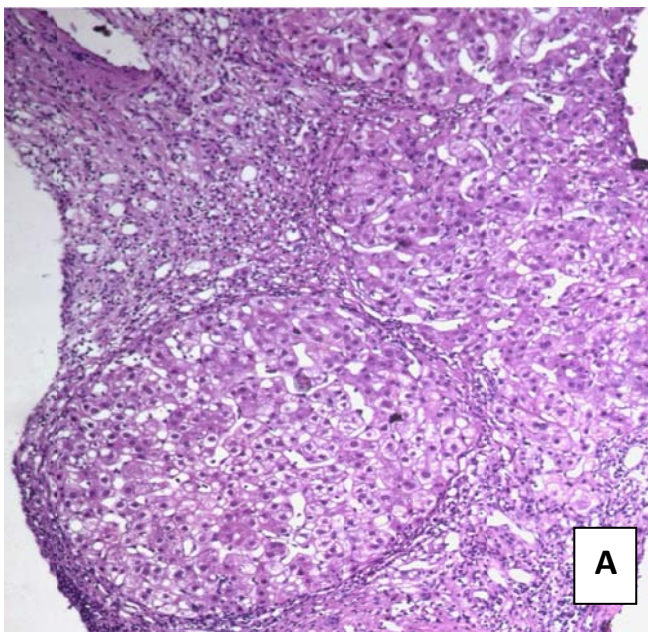
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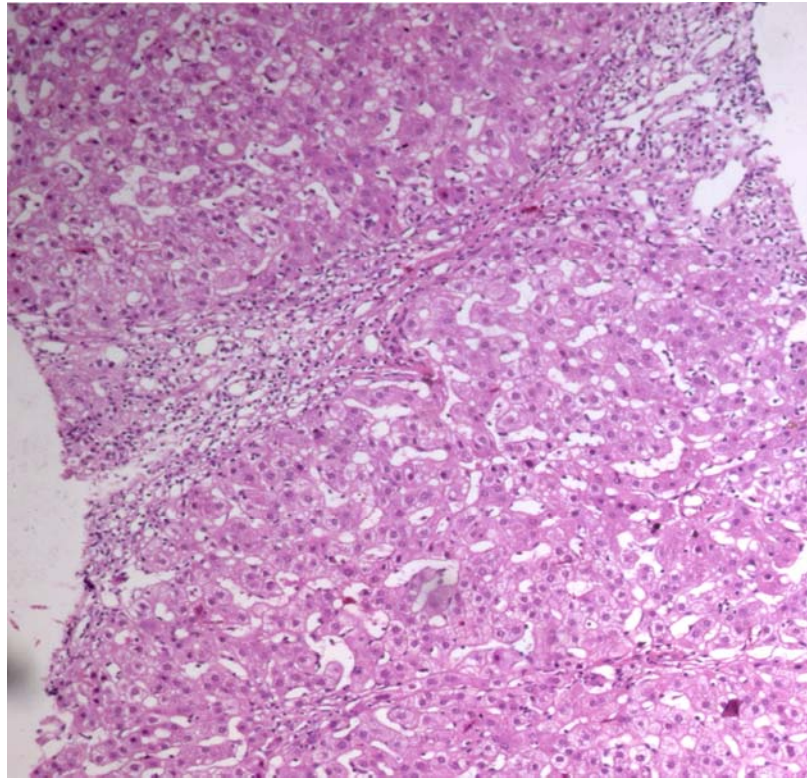
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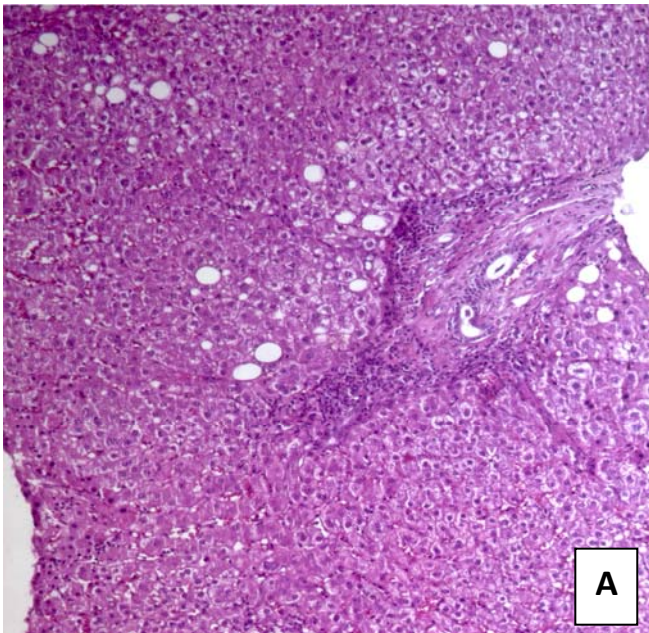
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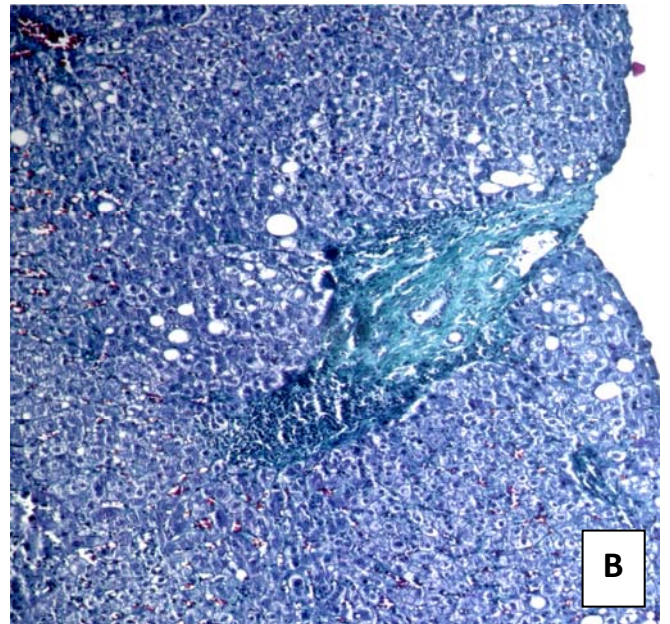
Side.2 : A) Liver sections from a case of chronic HCV A2 F4 showing a cirrhotic nodule rimmed by fibrous bands entangling mild number of chronic inflammatory cells (H & E, X100). B) same section stained with Masson Trichrome (X100).



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A



B

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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, ANGIO upregulates the transforming growth factor beta 1 expression *via* AT-II type 1 receptor (AT1R) *in vitro* (*Battaller 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 ANGIO are mediated through AT1R is related to the therapeutic interventions, since AT1R can be completely blocked by losartan, a specific ANGIO receptor antagonist. For instance, ANGIO 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*).