

A Randomized Controlled Study of the Effect of AT₁ antagonist on Fibrosis Markers in HCV Egyptian Patients

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ABSTRACT

AIM: The aim of this study was to evaluate the effect of telmisartan and losartan on liver functions and fibrosis markers in patients with chronic hepatitis C.

METHODS: Sixty patients were randomized into 3 groups. All groups received pegylated interferon α -2a and ribavirin. Telmisartan has been added to the first group and losartan has been added to the second group for the first 12 weeks of therapy. Blood samples have been collected before starting the treatment and after 12 weeks for counting of blood cells and measurement of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), α -2macroglobulin, and transforming growth factor beta (TGF- β ₁). Urinary hydroxyproline has been estimated.

RESULTS: Early virological response showed no significant difference between groups ($p > 0.05$). All groups had a significant decrease in serum ALT and α -2macroglobulin compared to pretreatment values. Telmisartan group showed a significant reduction in serum AST, GGT, TGF- β , and urinary hydroxyproline compared to control. Patients treated with telmisartan and losartan suffered significantly less leucopenia and thrombocytopenia than control patients ($p < 0.05$).

CONCLUSION: Addition of telmisartan to pegylated interferon and ribavirin may have a hepatoprotective, anti-fibrotic, and bone marrow stimulating effects in patients with chronic hepatitis C.

INTRODUCTION

HCV infection is a worldwide health problem^[1]. Liver fibrosis is the main determinant of HCV-related morbidity and mortality^[2]. Apart from the anti-viral effect, several evidences suggested that interferon (IFN) could improve liver fibrosis. However, the histological improvement could be observed only in patients who accomplish sustained virological response (SVR)^[3]. Combination of interferon with anti-fibrotic agents may provide synergistic effects^[4].

It has been reported that inhibition of rennin angiotensin system (RAS) significantly attenuated liver fibrosis development in several experimental models^[5]. Telmisartan is an angiotensin II receptors type 1 (AT₁) antagonist which can activate peroxisome proliferator activated receptors gamma (PPAR γ)^[6]. Telmisartan markedly attenuated hepatic fibrosis in a rat model of non alcoholic steatohepatitis (NASH)^[7], and CCl₄ induced hepatic fibrosis^[8]. Also, telmisartan had expressed an anti-fibrotic effect in hypertensive patients with NASH^[9]. The aim of this study was to evaluate the effect of telmisartan and losartan on liver functions and fibrosis markers in patients with chronic hepatitis C.

PATIENTS AND METHODS

Study design

This study has been done at the outpatient clinics of Kafr El-Sheikh Liver Research Center and Tanta University Hospitals from May 2008 to December 2009. Patients were subjected to different investigation including clinical investigation, laboratory analysis and liver biopsy within 1 to 5 d. the eligibility of the patients to the study

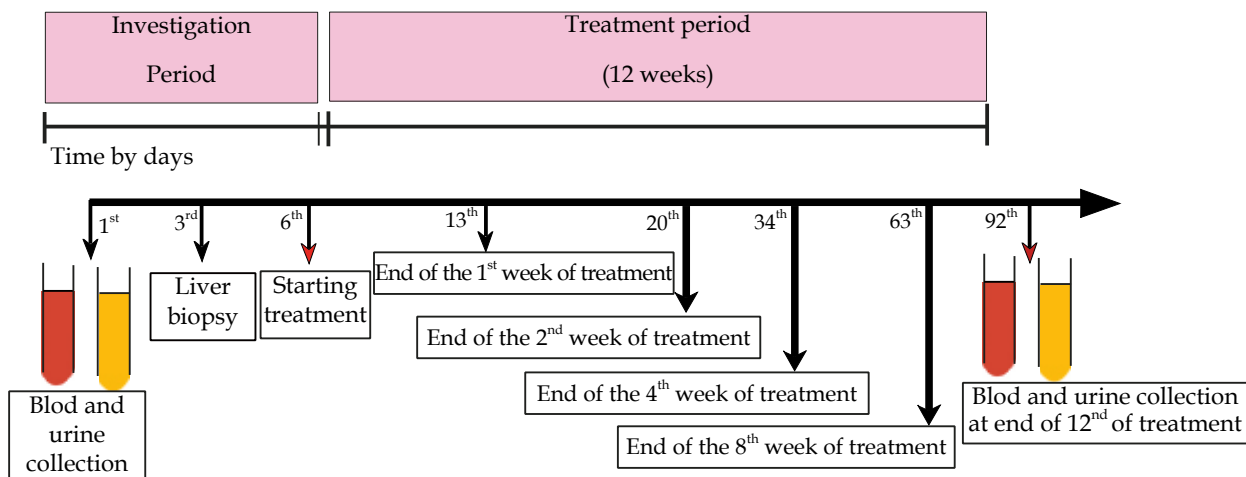


Figure 1 Study design showing an investigation period from day 1 to day 5 followed by treatment period for consecutive 12 weeks from day 6 to day 92. Patients were informed to return to the clinic at the end of the 1st, 2nd, 4th, 8th and 12th weeks of treatments.

were determined based on the results of these investigation. Sixty eligible patients with chronic hepatitis C were randomized using a computer generated list into 3 groups. All patients were treated with pegylated interferon α -2a 180 μ g subcutaneously weekly and ribavirin 15 mg/kg orally daily. Telmisartan (40 mg/d/orally) was added to the first group of patients (telmisartan group) and losartan (50 mg/d/orally) was added to the second group of patients (losartan group) for the first 12 weeks of therapy. The third group of patients have been treated with standard of care only (control group). All drugs pegylated interferon α -2a, ribavirin, telmisartan and losartan started at the 6th day of the study (Figure 1).

Informed consent has been signed and dated by every patient before the study. The study protocol has been approved by the institutional review board of the Faculty of Pharmacy, Tanta University, Tanta, Egypt. The study was conducted in conformity with ethical and human principles.

Selection of patients

Medical history was taken before starting any investigation with stress on schistosomiasis, bleeding attacks, smoking, alcohol intake, hypertension and diabetes.

Patients were excluded if they were unable to take oral medications; were pregnant, breast-feeding females; had a history of alcoholism or alcohol consumption of more than 40 g/d; had acute hepatitis A or were co-infected with HBV; had any alternative cause of liver disease; had a history of hypersensitivity or intolerance to losartan or telmisartan or were clinically unstable or had any concomitant condition that, in the opinion of the investigator, would preclude participation in this trial. Sexually active patients were informed to use birth control during and six month after last dose of interferon and ribavirin.

Patients enrolled in this study were adults of both sexes of age (20-60). All patients were infected with HCV genotype 4 with detectable serum HCV RNA in their blood. All patients were normotensive (Systolic pressure was in the range (110-140 mmHg) and diastolic pressure was in the range (70-100 mmHg).

Only Patients with Controlled diabetes defined as active treatment for diabetes with blood glucose values generally <120 mg/dL were accepted in this study. Diabetic patients enrolled in this study were treated with insulin.

Liver biopsies obtained from patients within 3 months of randomization showing findings compatible with chronic hepatitis C were accepted for this study. Two slides prepared from patients' liver

biopsy were examined by one pathologist. Patients' liver biopsies showed fibrosis scores between 1 and 5 according to Ishak scores^[9]. Cirrhotic patients were excluded from the study.

Fibrosis scores of patients liver biopsies was correlated to fibrotic markers [urinary excretion of hydroxyproline, serum level of α -macroglobulin, transforming growth factor beta (TGF- β 1) and serum gamma glutamyl transferase (GGT) before starting treatments.

Study schedule and surveillance parameters

After selection, the enrolled patients started treatment. They were asked to return to the clinic five times at the end of 1st, 2nd, 4th and 8th and 12nd weeks from starting treatment (Figure 1).

During each visits patients were clinically examined, blood pressure were measured, blood sample were collected for monitoring liver function [alanine aminotransferase (ALT), aspartate aminotransferase (AST), total and direct bilirubin], kidney function (serum creatinine) and counting of blood cells. In addition, patients were asked about any undesirable or irritable adverse event. At the end of the 12th week patients were asked to give urine sample in addition to blood sample and routine examination as previous visits.

In each visit patients were asked to give the remain of the provided drugs for compliance calculation. Patients whose compliance was less than 75% in any visit were excluded.

Laboratory analysis

Blood and urine samples were collected before treatment and after 12 weeks. Neutrophils, red blood cells, and platelets were counted automatically on a hematology analyzer (Sysmex KX-21, Japan).

ALT, AST, albumen, alkaline phosphatase (ALP), bilirubin, blood sugar, serum creatinine, prothrombin time, alpha-fetoprotein and thyroid stimulating hormone (TSH) were done according to kit instructions.

HCV RNA was determined using RT-PCR technique using QIAamp[®] viral RNA kit (QIAGEN, Germany).

Liver biopsy

The percutaneous liver biopsy technique was performed in all cases according to Grant and Neuberger^[10]. All biopsies were fixed, paraffin embedded and stained with hematoxylin and eosin. Grading of the necroinflammatory activity and staging of fibrosis was assessed according to modified histological activity index (Ishak *et al*, 1995)^[11].

Assay of fibrotic markers

Urinary excretion of hydroxyproline: 1mL of urine was hydrolyzed in 1.5 mL of 10 N HCl (final concentration is 6 N HCl). Tubes were then well closed and left in an oven at 110 °C for 12 h. The hydroxyproline content in the hydrolysate was measured according to Battaler *et al.*^[12].

Human α_2 -macroglobulin: Human α_2 -macroglobulin was quantitatively measured in fully automated turbidimetric system (Turbi-quick, Italy).

Transforming growth factor TGF- β_1

TGF- β_1 was assayed using Enzyme Linked-Immuno-Sorbent Assay (ELISA) according to the kit instructions (Biosource, Belgium)^[13].

Statistical analysis

Statistical analysis was performed using SPSS for windows version 15. The data were parametric by using Kolmogorov-smirnov test. Results were expressed as mean \pm standard error (SE). Baseline data were compared using one way analysis of variance (ANOVA). Paired *t*-test was used to assess the change in parameters before and after treatment. Proportions were compared using Fisher's exact test (two-sided). F-test was used to compare between groups. Pearson correlation coefficient was used to study correlation between variable. Significance was considered when *p* value was less than 0.05.

RESULTS

IV-1 Patients Characteristics

All patients were matched as regards age and sex (Table 1). Baseline biochemical indices and blood cells count were not significantly different between all groups (Table 1). Measuring serum level of TSH and α -fetoprotein revealed that all patients had normal levels of both parameters (Table 1)

Patients showed non significant differences concerning hepatic fibrosis scores and fibrotic markers at baseline (Table 2). All patients enrolled in this study were normotensive. They were matched as regard to both systolic and diastolic pressure (Table 3). Baseline HCV-RNA revealed that all patients had moderate viremia with no significant difference between all groups (Table 4).

Effect of AT₁ antagonists on blood pressure

Only telmisartan treated patients showed a significant decrease in systolic and diastolic blood pressure compared to baseline level (*p*<0.05) while losartan treated and control patients expressed a non significant changes (Table 5) with on significant differences between groups.

Effect of AT₁ antagonists on virological response

Rapid virological response (RVR) was 52% in telmisartan and losartan groups while it was 55% in control group with no significant difference between groups. Early virological response (EVR) was 75% in telmisartan group, and 70% in the two other groups with no significant difference between groups (Figure 2).

Effect of AT₁ antagonists on biochemical liver function

All patients included in the study showed significant decrease in ALT compared to baseline levels. Telmisartan treated patients had a significant decrease in AST compared to baseline levels and other groups (Figure 3). Telmisartan treated patients showed a significant decrease in bilirubin while losartan treated patients and control group

patients showed non significant decreases compared to baseline levels with no significant difference between groups (Figure 3).

Effect of AT₁ antagonists on blood cells count

Telmisartan and losartan treated patients showed less reduction in platelets, total leukocytic count (TLC) and absolute neutrophilic count (ANC) than patients in the control group. The difference was statistically significant (*p*<0.05) (Figure 4).

Effect of AT₁ antagonists on fibrosis markers

Telmisartan treated patients showed a significant decrease in urinary excretion of hydroxyproline and serum GGT compared to control group (Figure 5).

All patients showed significant decreases in α_2 -Macroglobuline and TGF- β_1 serum levels. Only telmisartan treated patients showed a significant decrease in TGF- β_1 serum level compared to control (Figure 5).

Correlation of fibrosis markers with Ishak fibrosis score of liver biopsy

Urinary excretion of hydroxyproline, α_2 -macroglobulin, TGF- β_1 and serum GGT showed a significant correlation with Ishak fibrosis score of liver biopsies of patients enrolled in this study (Table 6).

Table 1 Baseline data of HCV patients.

	Telmisartan group	Losartan group	Control group
N	20	20	20
AGE	42.1 \pm 4.13	37.7 \pm 3.31	36.8 \pm 2.8
Sex (male/ female)	14/6	15/5	13/7
Smoking (Yes /No)	(6/14)	(9/11)	(5/15)
BMI(kg/m ²)	27.6 \pm 1.6	24.6 \pm 1.4	27 \pm 0.83
ALT(u/L)	68.14 \pm 4.9	57.89 \pm 6.2	54.8 \pm 5.7
AST(u/L)	75.25 \pm 8.4	67.71 \pm 7.87	55.67 \pm 9.21
ALP (u/L)	92.9 \pm 6.95	89.67 \pm 6.52	77.9 \pm 6
Albumen (g/dL)	4.58 \pm 0.08	4.33 \pm 0.13	4.56 \pm 0.07
Prothrombin activity (%)	88.5 \pm 0.02	85.8 \pm 0.03	93 \pm 0.01
Total bilirubin (mg/dL)	0.89 \pm 0.1	0.88 \pm 0.1	0.68 \pm 0.067
Direct bilirubin (mg/dL)	0.25 \pm 0.02	0.24 \pm 0.03	0.25 \pm 0.02
Serum Creatinine (mg/dL)	0.86 \pm 0.06	0.95 \pm 0.09	0.77 \pm 0.05
Fasting Blood glucose level mg/dL	121.17 \pm 31.4	91.11 \pm 5.4	88.17 \pm 2.8
Platelet count (1000 cell/mm ³)	234.1 \pm 8.7	215.1 \pm 17.33	250.8 \pm 5.21
TLC (cell/mm ³)	6593 \pm 524	6155 \pm 376	7113.6 \pm 393
ANC (cell/mm ³)	3422 \pm 629	2555 \pm 607	3528 \pm 441
RBCs count (1000 cell/mm ³)	5216 \pm 277.8	5022 \pm 134.6	5141 \pm 124.3
Hemoglobin (gm /dL)	14.4 \pm 0.7	13.9 \pm 0.5	14.6 \pm 0.3
TSH (mIU/L)	1.63 \pm 0.38	1.58 \pm 0.27	1.56 \pm 0.23
α -feto protein (ng/mL)	7.52 \pm 3.09	5.5 \pm 1.87	2.64 \pm 0.4

Data are expressed as Mean \pm SE; There was non significant difference between all groups.

Table 2 Baseline fibrosis score and fibrotic markers levels of HCV patients.

	Telmisartan group	Losartan group	Telmisartan group
Early fibrosis (Ishak 1,2,3)#	12(60%)	14 (70%)	12(60%)
Advanced fibrosis (Ishak 4,5)#	8 (40%)	6 (30%)	8 (40%)
Low Histological activity index (0-9)#	4(20%)	12 (60%)	4(20%)
High Histological activity index (10-18)#	16(80%)	8(40%)	16(80%)
GGT (u/L)	50 \pm 7.9	47 \pm 6.8	50 \pm 7.9
α_2 -Macroglobuline (mg/L)	289.9 \pm 13.905	254 \pm 25.03	289.9 \pm 13.905
Hydroxyproline (μ g/mL)	577.6 \pm 41.78	509 \pm 102.43	577.6 \pm 41.78
TGF- β_1 (pg/mL)	18125 \pm 910	15144 \pm 1655	18125 \pm 910

Data are expressed as Mean \pm SE; # Data are expressed as number of patients (% of patients compared to total No of patients in each group); There was non significant difference between all groups.

Table 3 Baseline systolic and diastolic blood pressure of HCV patients.

	Telmisartan group	Losartan group	Control group
Systolic pressure (mmHg)	128.7±2.6	123.33±2.35	124.37±3.1
Diastolic pressure (mmHg)	89±3.5	81.1±2	84.17±1.9

Data are expressed as Mean±SE; There was non significant difference between all groups.

Table 4 Baseline HCV-RNA serum level of HCV patients.

	Telmisartan group	Losartan group	Control group
HCV Ab Positive			
HCV-RNA	488723±126258	454992±266137	955500±267456

Data are expressed as Mean ± SE; There was non significant difference between all groups.

Table 5 Effect of AT₁ antagonists on blood pressure in HCV patients.

	Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)	
	Baseline pressure	After 12w	Baseline pressure	After 12w
Telmisartan group	128.75±2.6	116.3±4.4*	89±3.5	78±3.8*
Losartan group	123.33±2.35	121.11±2	81.1±2	80±1.4
Control group	124.37±3.1	121.25±2.2	84.17±1.9	81.66±1.1

Telmisartan group: Patients were treated with pegylated interferon α_{-2a} 180 μ g/week and ribavirin 15 mg/kg/d and telmisartan 40 mg/d for 12 weeks; Losartan group: Patients were treated with pegylated interferon α_{-2a} 180 μ g/week and ribavirin 15 mg/kg/d and losartan 50 mg/d for 12 weeks; Control group: Patients were treated with pegylated interferon α_{-2a} 180 μ g/week and ribavirin 15 mg/kg/d for 12 weeks; * Significant compared to baseline ($p \leq 0.05$); Data are expressed as Mean±SE; N=20.

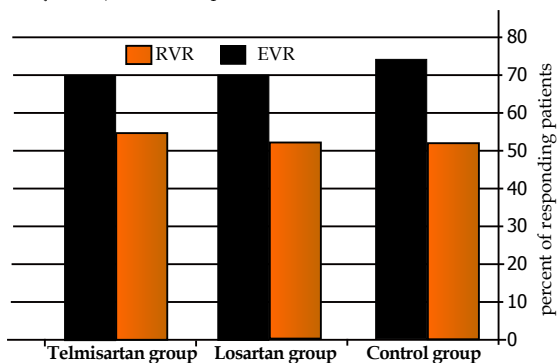


Figure 2 HCV patients were treated with pegylated interferon α_{-2a} 180 μ g weekly and ribavirin 15 mg/kg/d with either telmisartan (40 mg/d); (telmisartan group) or losartan (50 mg/d) (losartan group) for 12 weeks. Control patients were treated with pegylated interferon α_{-2a} 180 μ g weekly and ribavirin 15 mg/kg/d only; Data are expressed as % of responders among each group; N=20.

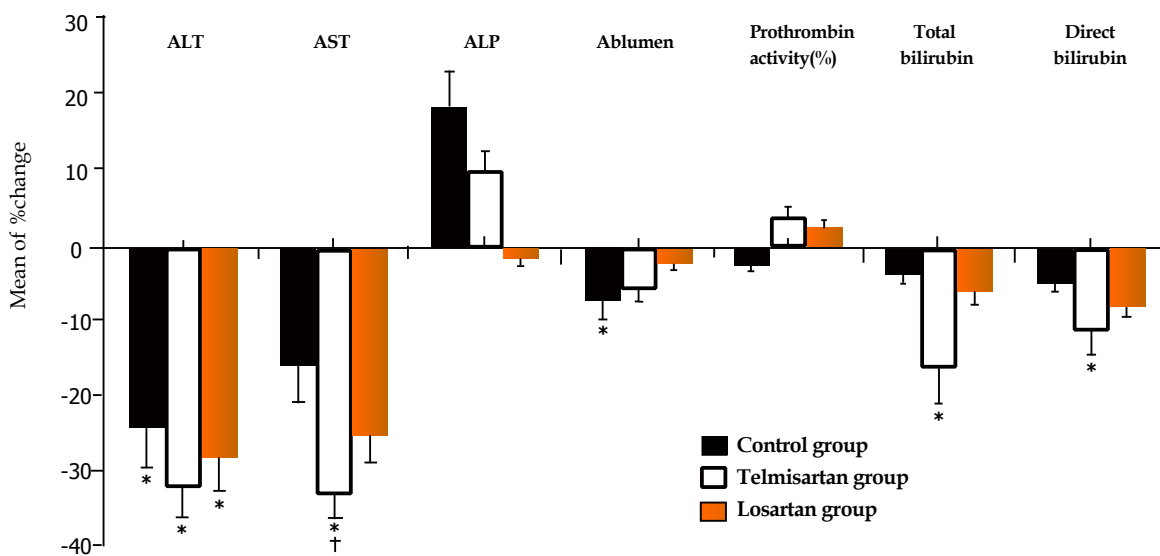


Figure 3 HCV patients treated with pegylated interferon α_{-2a} 180 μ g weekly and ribavirin 15 mg/kg/d with either telmisartan (40 mg/d) (telmisartan group) or losartan (50 mg/d) (losartan group) for 12 weeks. Patients in control group were treated with pegylated interferon α_{-2a} 180 μ g weekly and ribavirin 15 mg/kg/d only for 12 weeks. Data are expressed as Mean of % change compared to baseline±SE; Data are expressed as Mean±SE; N=20. * Significant compared to baseline ($p \leq 0.05$); † Significant compared to control patients ($p \leq 0.05$); ‡ Significant compared to losartan treated patients ($p \leq 0.05$).

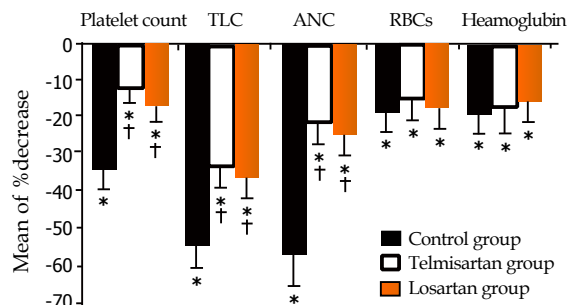


Figure 4 HCV patients treated with pegylated interferon α_{-2a} 180 μ g weekly and ribavirin 15 mg/kg/d with either telmisartan (40 mg/d) (telmisartan group) or losartan (50 mg/d) (losartan group) for 12 weeks; Patients in control group were treated with pegylated interferon α_{-2a} 180 μ g weekly and ribavirin 15 mg/kg/d only for 12 weeks. Data are expressed as Mean of % change compared to baseline±SE. N=20; * Significant compared to baseline ($p \leq 0.05$); † Significant compared to control patients ($p \leq 0.05$).

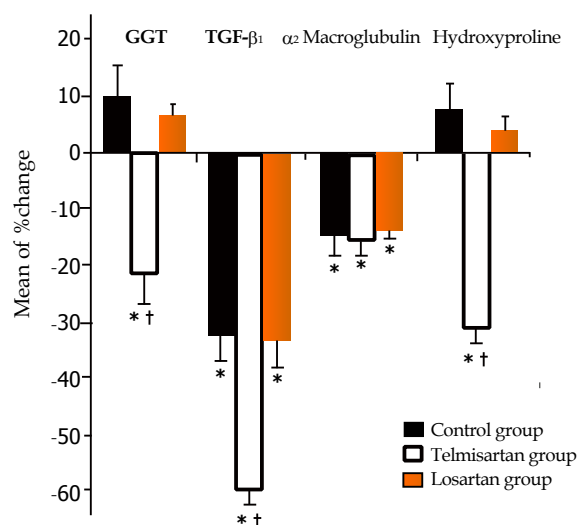


Figure 5 HCV patients treated with pegylated interferon α_{-2a} 180 μ g weekly and ribavirin 15 mg/kg/d with either telmisartan (40 mg/d) (telmisartan group) or losartan (50 mg/d) (losartan group) for 12 weeks; Patients in control group were treated with pegylated interferon α_{-2a} 180 μ g weekly and ribavirin 15 mg/kg/d only for 12 weeks; Data are expressed as Mean ±SE; N=20; * Significant compared to baseline ($p \leq 0.05$); † Significant compared to control patients ($p \leq 0.05$).

Table 6 Correlation of Ishak fibrosis score and baseline serum fibrotic markers.

Fibrotic markers	r
GGT (u/L)	0.678*
α 2-Macroglobuline (mg/L)	0.803*
Hydroxyproline (μ g/mL)	0.745*
TGF- β ₁ (pg/mL)	0.917*

*Significant correlation ($p \leq 0.05$); Urinary excretion of hydroxyproline, α 2-macroglobulin, TGF- β ₁ and serum GGT showed a significant correlation with Ishak fibrosis score of liver biopsies; N=60.

DISCUSSION

RAS-inhibitory agents exerted anti-fibrotic effects in several types of chronic liver diseases, including hepatitis C^[14,15]. Despite the large number of animal studies, there is a relative paucity of human data to support the use of these drugs in human liver disease^[16]. This study investigated the effect of telmisartan and losartan on hepatic fibrosis in HCV patients treated with pegylated interferon and ribavirin.

In the current study, telmisartan augmented pegylated interferon α -2a hepatoprotective effect expressed as significant reduction in ALT and AST serum level. Our results were consistent with Yoshiji *et al* 2006^[4], who reported that interferon monotherapy decreased ALT and that ACE inhibitors augmented this hepatoprotective effect in hepatitis C patients.

Liver fibrosis is the main determinant of HCV-related morbidity and mortality^[2]. In this study hepatic fibrosis was assayed using four markers, urinary hydroxyproline, serum level of GGT, TGF- β ₁ and α 2-macroglobulin. These parameter were significantly correlated with Ishak fibrosis score of liver biopsies of patients enrolled in this study.

α 2-macroglobulin serum level showed a very good correlation with histological stages in patients with hepatitis C and B^[17]. Moreover, It is the most useful single test predicting hepatic fibrosis among other markers included in the fibrotest^[18].

TGF- β ₁ is considered as a pivotal inducer of liver fibrosis acting through activation of hepatic stellate cells (HSCs) and their transformation to myofibroblasts, which are the main source of extracellular matrix proteins^[19].

Our results revealed that addition of telmisartan but not losartan to pegylated interferon and ribavirin significantly decreased serum level of GGT as well as urinary excretion of hydroxyproline. Also, telmisartan increased the inhibitory effect of pegylated interferon and ribavirin on TGF- β ₁ serum level.

In other studies, losartan has been found to have an antifibrotic effect in HCV patients whether given alone or combined with ursodeoxycholic acid^[14,15]. However these studies had been conducted for longer period (at least six months) compared to our study 12 weeks. We have conducted a preliminary study for only 4 weeks, the preliminary data revealed that 4 weeks is too short time for both telmisartan and losartan to exert antifibrotic activity (Data are not shown).

Our study detect the early antifibrotic effect of AT₁ blocker however longer studies may be useful to illustrate the effect of these agent on sustained viral response (SVR) in hepatitis C patients. Longer studies may also demonstrate the tolerability of AT₁ blocker for chronic use in normotensive hepatitis C patients

In consistency with our results, Georgescu *et al*^[9] reported that telmisartan but not valsartan improved fibrosis score in NASH patients via its PPAR- γ effect. PPAR- γ may represent potential therapeutic targets in HCV infection^[20].

Jin *et al*^[7] provided evidence that telmisartan was able to reverse activated HSCs into quiescent state through inhibition of AT₁ receptors and activation of PPAR- γ in the liver.

The effect of telmisartan on TGF- β ₁ may be in part PPAR- γ dependent where the PPAR- γ antagonist GW9662 blocked the inhibitory effect of telmisartan on TGF- β ₁ induced accumulation of extracellular matrix on kidney^[21].

The antifibrotic effect of interferon was supported by another study reported that pegylated interferon- α 2b and ribavirin induce a significant decrease in TGF- β ₁, TIMP-1, and MMP-1 serum concentrations of HCV patients^[19].

Interferon and ribavirin combination therapy is associated with hematologic abnormalities such as anemia, neutropenia, and thrombocytopenia^[22]. An interesting finding of our study was that both telmisartan and losartan ameliorated hematopoietic abnormalities induced by pegylated interferon.

This was in accordance with Charrier *et al*^[23] who demonstrated that perindopril and telmisartan accelerated hematopoietic recovery and led to a significant increase in platelet and red cell counts in irradiated mice. They have also found that pretreatment with perindopril increased bone marrow cellularity and the number of hematopoietic progenitor cells after irradiation.

Although AT₁ antagonists may act as negative regulators of hematopoiesis those drugs may exert myeloprotective effects by mediating G0/G1 arrest^[24]. In this way, they may prevent DNA breakage during the S phase and subsequent cell apoptosis^[23].

According to our results, both losartan and telmisartan appear to be well tolerated with no significant side effect. No patient had a hypotensive shock. The reported side effect during the study period was headache and drowsiness with both telmisartan and losartan.

Different studies reported the safety and tolerability of same doses of losartan and telmisartan in normotensive patients^[25,26].

In conclusion, telmisartan but not losartan improved the effect pegylated interferon and ribavirin on fibrosis markers. The partial PPAR- γ activity of telmisartan could illustrate its antifibrotic activity which could not be achieved by the AT₁ antagonist losartan. AT₁ antagonists appeared to be safe and well tolerated in normotensive HCV patients. Furthermore, combining either losartan or telmisartan with pegylated interferon and ribavirin has been found to decrease interferon induced myelotoxicity may be via AT₁ blocking dependent mechanism.

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