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Impact of Losartan on Hepatic Fibrosis in Hepatitis C Virus Egyptian Patients with Advanced Fibrosis who Achieved Sustained Virological Response after Direct Acting Antivirals

Mohamed Yacoub[1*], Mahmoud Abdo[2], Mohammad El-sayed[2], Mohamed Hassany[1], Gamal Esmat[2]

[1] Hepatology and Gastroenterology Department, National Hepatology and Tropical Medicine Research Institute, Cairo.

[2] Endemic Medicine department, Cairo University

Corresponding author: Mohamed Yacoub

Email: mohamedamrnasr@icloud.com

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Abstract:

Background: Hepatitis C virus (HCV) infection is a significant global health concern, affecting over 184 million individuals worldwide, which carries the risk of progression to hepatic fibrosis, cirrhosis. With a better understanding of pathogenesis of fibrosis, an increasing number of potential antifibrotic drugs are under trials.

Aim: To evaluate the impact of one-year Losartan administration on liver fibrosis in HCV patients with advanced fibrosis who achieved sustained virological response following Direct Acting Antivirals therapy.

Patients and Methods: The prospective investigation involved 120 adult Egyptian cases who had advanced liver fibrosis confirmed by transient elastography using the FibroScan (scores F3-F4) and by one of the other non-invasive fibrosis scores (FIB4). Cases have been recruited through the Kasr Alainy viral hepatitis center, affiliated with the National Committee for Control of Viral Hepatitis (NCCVH).

Results: Our results showed tendency of losartan to reverse liver fibrosis, however, the threshold of statistical significance was not reached, results also showed significant decrease in the systolic and diastolic blood pressure in the losartan-treated group reflecting the known antihypertensive properties of the drug, In addition, the platelet count in the treated group exhibited significant increase which could be secondary to decreased portal venous pressure induced by losartan, Losartan significantly decreased ALT and AST, and increased serum albumin level at 12 months suggestive of further architectural and functional recovery of the liver. Additionally, there was significant reduction in the Fib-4 score in both groups.

Conclusion: Losartan doesn't have a potent antifibrotic effect in patients with advanced liver fibrosis. Losartan has an established safety profile in compensated liver cirrhosis patients. It may promote a better outcome in early fibrosis stages. Losartan may improve synthetic liver functions and platelets in compensated cirrhotic patients.

Keywords: Hepatitis C virus, liver fibrosis, Losartan.

1. Introduction

Hepatitis C infection is a significant worldwide health problem, affecting approximately 184 million individuals globally. Egypt has a significantly high occurrence rate for hepatitis C infection compared to other countries in the world. The 2015 National Demographic Health Survey (EDHS) showed a significant decrease in the number of hepatitis C cases to six million, compared to approximately ten million in 2008. Inspite of this obvious decrease, the significant number of cases in a resource-constrained nation such as Egypt continues to pose significant national health and economic challenge **(1)**.

Liver fibrosis is an intricate and ever-changing process that results in the accumulation of matrix proteins, including collagen, elastin, and proteoglycans, in the liver. Throughout the process of fibrogenesis, hepatic stellate cells are stimulated by pro-inflammatory cytokines and undergo a transformation into hepatic myofibroblasts (HMS). These hepatic myofibroblast cells are responsible for producing the majority of matrix proteins in the liver **(4)**.

The availability of safe, effective, and well-tolerated therapy significantly increases the chances of achieving successful control / eradication of HCV management, as outlined in the hepatitis C elimination plans of the WHO. In general, direct-acting antiviral treatment regimens effectively eliminate hepatitis C infection in more than 95% of treated individuals **(2)**.

Compelling clinical evidences indicate that - clearance of HCV or long-term effective suppression of HBV, using potent nucleotide analogs (NAs), significantly decrease and potentially reverse the advancement of cirrhosis and fibrosis **(3)**.

In this study we aimed to assess the impact of one-year Losartan administration on the structural and functional markers of the liver in HCV cases with advanced fibrosis who achieved SVR following DAAs management.

Patients and methods

The prospective investigation involved 120 adult Egyptian cases who had advanced liver fibrosis, as proved by transient elastography using the FibroScan to be (F3-F4) and by one of the other non-invasive fibrosis scores as FIB4 (Age [yr] x AST [U/L])/(PLT [10(9)/L]) x (ALT [U/L]) to be >3.25, one year following SVR after HCV treatment with DAAs. Cases have been recruited from the Kasr Alainy viral hepatitis center, affiliated with the National Committee for Control of Viral Hepatitis (NCCVH). As showing in Fig 1, **cases have been randomized into two groups:** the Losartan Group (A) included 60 patients who were given Losartan 50 mg (Cozaar, MSD) once daily for 12 months, and the Control Group (B) included 60 patients who were given no medications and followed for 12 months.

Inclusion criteria: age 18–70 years, BMI <30, and compensated cirrhosis (child A).

Exclusion criteria: hypersensitivity to losartan, pregnancy or breast feeding, decompensated cirrhosis, elevated liver enzymes more than twofold, hypotension less than 90/60, patients already on losartan, chronic kidney disease, and hyperkalemia.

Methods

All patients were subjected to the following prior to treatment: detailed history taking, blood pressure measurement, descriptive data (age, body mass index (BMI), gender, and blood samples for CBC, Creatinine, INR, total bilirubin, AST, ALT, ALP, albumin, and AFP were obtained. Quantitative HCV PCR; US examination of the abdomen, FIB 4 scoring, transient elastography by the FibroScan device (EchoSens, Paris, France), and upper endoscopy if fibrosis > 19.2 kPa (according to the National Committee for Control of Viral Hepatitis protocol) or presence of portal vein dilatation and splenomegaly by abdominal ultrasound.

During and post treatment

The safety and tolerability assessment for the losartan group was done using a predesigned sheet for gathering reported AEs, as well as monitoring renal function tests and vital signs every two weeks for one month at the beginning of treatment. **All patients were followed after six and twelve months for:** blood pressure measurement; full clinical examination; liver biochemical profiling; serum creatinine; Complete blood count, INR, AFP and abdominal ultrasonography, In addition to Fibroscan and FIB 4 score at twelve months.

Ethical considerations

The procedures, which include those that involve human subjects, have been carried out in accordance with the ethical criteria established by the institutional and/or national research committee, as well as the 1964 Helsinki Declaration and its subsequent revisions or similar ethical standards. The investigation Ethics Committee granted sanction for the investigation to be performed at the Faculty of Medicine, Cairo University. In order to participate in the trial and authorize the dissemination of their anonymized data, all patients submitted written informed consents. We confirm that the data has been entirely anonymized.

Statistical Methods

The gathered data have been encoded, organized into tables, and subjected to statistical analysis by IBM SPSS statistics software version 28.0 [IBM Corp.]. The quantitative data were assessed for normality by the Kolmogorov-Smirnov test. The means, standard deviations,, and the minimum and maximum values were calculated. Data were subsequently compared using the independent t-test for two independent groups, the RMANOVA test for three dependent variables, and the paired t-test for two dependent variables. Qualitative data is represented as numerical values and percentages and are analyzed using Chi square and Fisher’s exact tests for two independent groups. Additionally, the marginal homogeneity test is used for dependent multinomial variables. The level of significance was set at a p-value of less than 0.050.

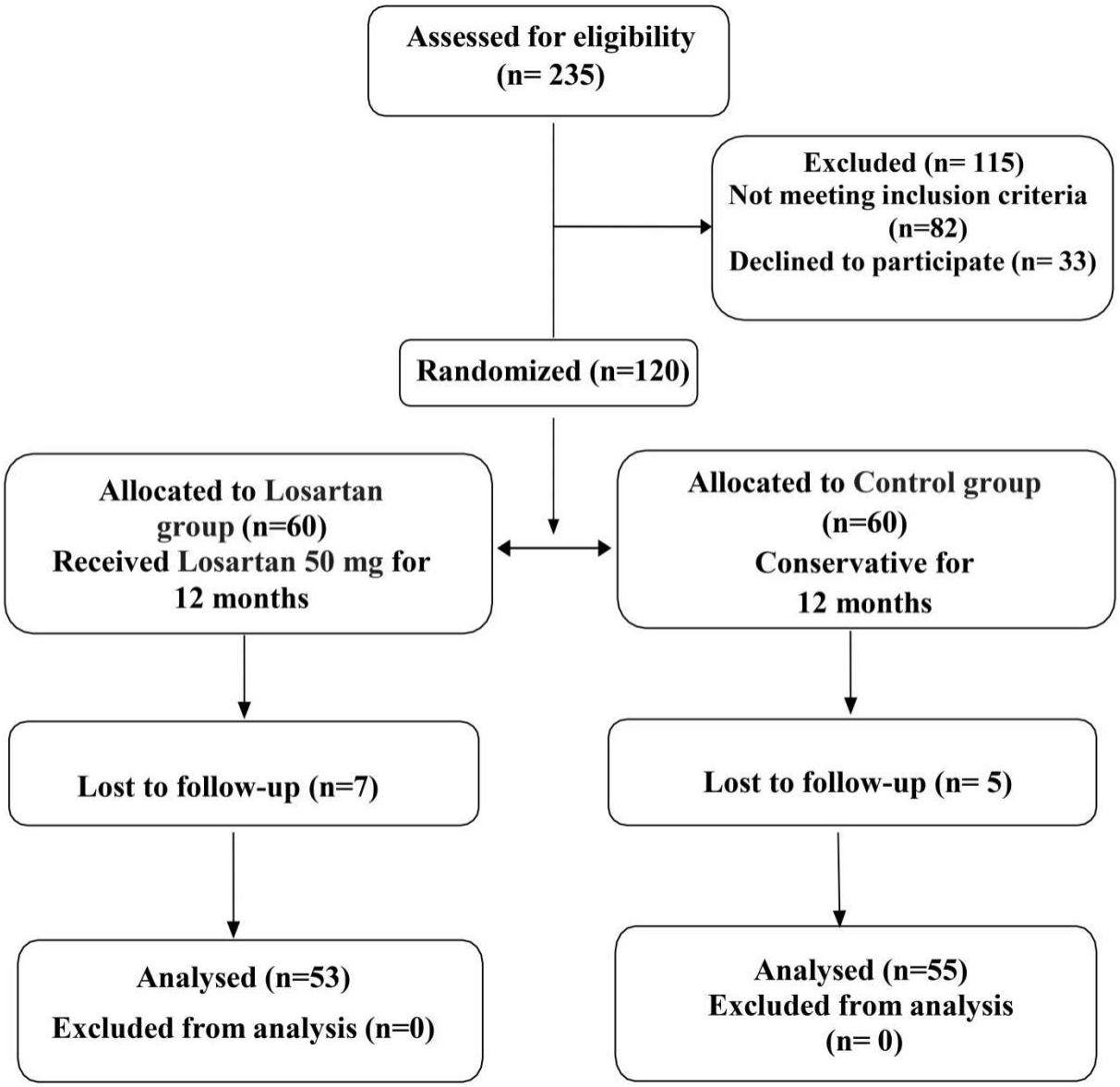

Figure (1): Flow chart of investigation participants

Results:

1- Demographic makeup of the studied groups:

There was no statistically significant variability in the studies groups in terms of the recorded demographic characteristics; gender, age, body mass index $p>0.05$. (Table 1)

Table (1): General characteristics among the groups of investigation

Variables	Measures	Losartan (Total=53)	Control (Total=55)	p-value
Age (years)	**Mean ± standard deviation**	52.4±10.5	53.5±6.8	^0.480
	Range	28.0–68.0	32.0–68.0	
Gender (n, %)	**Male**	25 (47.2%)	29 (52.7%)	#0.564
	Female	28 (52.8%)	26 (47.3%)	
BMI (kg/m^2)	**Mean± standard deviation**	24.5±2.3	24.2±2.7	^0.504
	Range	20.0–29.5	20.0–29.5	

BMI: Body mass index. ^Independent t-test. #Chi square test.

2- Variations in the blood pressure among the studied groups:

As demonstrated in table 2, there was no statistical significant variances among the groups of study according to baseline Diastolic blood pressure and Systolic blood pressure p>0.05, then they became significantly lesser in Losartan group in month-6 and month-12. Systolic blood pressure & Diastolic blood pressure significantly reduced in Losartan group and non-significantly changed in control group p<0.001.

Table (2): Blood pressure changes among the groups of investigation

Variables	Time	Measures	Losartan (Total=53)	Control (Total=55)	p-value (Inter-groups)
Systolic blood pressure (mmHg)	**Baseline**	**Mean ± SD**	129.2±10.0	128.2±6.6	^0.553
		Range	110.0–150.0	115.0–145.0	
	Month-6	**Mean ± SD**	123.4±7.8	128.2±7.4	**<0.001***
		Range	110.0–140.0	115.0–145.0	
	Month-12	**Mean ± SD**	119.5±8.2	128.5±6.2	**^<0.001***
		Range	100.0–140.0	120.0–145.0	
	p-value (Intra-groups)		**¤<0.001***	¤0.564	
Diastolic blood pressure (mmHg)	**Baseline**	**Mean ± SD**	84.5±5.7	84.0±6.0	^0.642
		Range	70.0–100.0	70.0–100.0	
	Month-6	**Mean ± SD**	79.8±7.4	83.3±6.5	**^0.011***
		Range	70.0–95.0	70.0–95.0	
	Month-12	**Mean ± SD**	74.2±7.5	83.8±5.7	**^<0.001***
		Range	60.0–90.0	70.0–100.0	
	p-value (Intra-groups)		**¤<0.001***	¤0.237	

^Independent t-test. ¤RMANOVA test. *Significant.

3- Effect of Losartan on liver functions

Our results indicate (table 3) that ALT, AST and INR significantly decreased in Losartan group and in Control group p<0.05, but Albumin significantly increased in Losartan group and non-significantly changed in control group. Total bilirubin non-significantly changed in Losartan group and in Control group p>0.05.

Table (3): Liver function changes among the groups of investigation

Variables	Time	Measures	Losartan (Total=53)	Control (Total=55)	p-value (Inter-groups)
ALT (IU/L)	**Baseline**	**Mean±SD**	29.0±11.5	28.7±11.9	0.884
		Range	12.0–51.0	12.0–57.0	
	Month-6	**Mean±SD**	26.8±10.3	27.4±10.1	0.757
		Range	10.0–45.0	12.0–50.0	
	Month-12	**Mean±SD**	25.1±9.4	25.7±10.2	0.723
		Range	11.0–44.0	9.0–48.0	
	p-value (Intra-groups)		¤<**0.001***	¤**0.002***	
AST (IU/L)	**Baseline**	**Mean±SD**	38.0±10.9	37.8±12.4	0.744
		Range	19.0–65.0	18.0–71.0	
	Month-6	**Mean±SD**	30.2±13.0	31.3±13.5	0.843
		Range	11.0–55.0	10.0–61.0	
	Month-12	**Mean±SD**	28.2±12.0	29.3±13.4	0.643
		Range	10.0–50.0	10.0–55.0	
	p-value (Intra-groups)		¤<**0.001***	¤<**0.001***	
Total bilirubin (mg/dL)	**Baseline**	**Mean± standard deviation**	0.93±0.22	0.94±0.19	0.770
		Range	0.50–1.70	0.60–1.30	
	Month-6	**Mean± standard deviation**	0.93±0.18	0.95±0.21	0.652
		Range	0.60–1.60	0.60–1.50	
	Month-12	**Mean± standard deviation**	0.91±0.20	0.95±0.20	0.355
		Range	0.50–1.50	0.60–1.30	
	p-value (Intra-groups)		¤0.533	¤0.716	
Albumin (gm/L)	**Baseline**	**Mean± standard deviation**	3.7±0.4	3.6±0.4	0.673
		Range	2.9–4.8	2.9–4.6	
	Month-6	**Mean± standard deviation**	3.7±0.4	3.6±0.4	0.274
		Range	2.9–4.6	2.9–4.6	
	Month-12	**Mean± standard deviation**	3.9±0.4	3.6±0.4	**<0.001***
		Range	3.2–4.9	2.9–4.6	
	p-value (Intra-groups)		¤**<0.001***	¤0.083	
INR	**Baseline**	**Mean± standard deviation**	1.07±0.11	1.07±0.12	0.911

		Range	0.90–1.50	0.80–1.50	
	Month-6	**Mean± standard deviation**	1.08±0.14	1.08±0.14	0.966
		Range	0.90–1.50	0.80–1.40	
	Month-12	**Mean± standard deviation**	1.08±0.12	1.08±0.12	0.977
		Range	0.90–1.50	0.90–1.50	
	p-value (Intra-groups)		¤0.388	¤0.427	

^Independent t-test. ^RMANOVA test. *Significant.

4- Effect of Losartan on kidney functions

No statistically significant differences were observed among the study groups at baseline, month-6 and month-12; creatinine levels p>0.05. Creatinine significantly declined in Losartan group and in Control group. (Table 4)

Table (4): Creatinine changes among the groups of investigation

Variables	Time	Measures	Losartan (Total=53)	Control (Total=55)	p-value (Inter-groups)
Creatinine (mg/dL)	**Baseline**	**Mean± standard deviation**	0.92±0.19	0.93±0.17	^0.647
		Range	0.60–1.40	0.60–1.40	
	Month-6	**Mean± standard deviation**	0.92±0.12	0.91±0.14	^0.865
		Range	0.70–1.10	0.50–1.20	
	Month-12	**Mean± standard deviation**	0.85±0.14	0.88±0.16	^0.338
		Range	0.60–1.20	0.50–1.20	
	p-value (Intra-groups)		**¤0.001***	**¤0.001***	

5- Development of hepatocellular carcinoma

Again, there was no statistically significant differences relevant to hepatocellular carcinoma development among the study groups as calculated at month-12; p>0.05. (Table 5)

Table (5): Hepatocellular carcinoma among the studied groups

Time	Findings	Losartan (Total=53)	Control (Total=55)	p-value
Month-12	**Positive**	2(3.8%)	3 (5.5%)	§0.999
	Negative	51 (96.2%)	52 (94.5%)	

§Fisher's Exact test.

6- Changes in the fibrosis score

While the changes in the fibrosis score were statistically insignificant until 6 months post treatment, critically, the Fib-4 score, fibrosis (kpa) and the fibrosis grading significantly decreased in the Losartan and control groups at the 12 months' time point. (Table 6 and 7)

Table (6): Fib-4 score among the groups of study

Variables	Time	Measures	Losartan (Total=53)	Control (Total=55)	p-value (Inter-groups)
Fib-4 score	**Baseline**	**Mean± standard deviation**	4.5±1.6	4.9±2.3	^0.314
		Range	3.3–9.6	3.3–12.4	
	Month-6	**Mean±SD**	3.8±2.2	4.4±2.9	^0.294
		Range	1.4–11.2	1.5–13.2	
	Month-12	**Mean±SD**	3.3±1.6	4.5±3.0	**^0.014***
		Range	1.4–9.4	1.5–15.0	
	p-value (Intra-groups)		**¤<0.001***	**¤0.047***	

^Independent t-test. ^RMANOVA test. *Significant.

Table (7): Fibroscan Reedings among the groups of study

Variables	Time	Measures	Losartan (Total=53)	Control (Total=55)	p-value (Inter-groups)
Fibrosis (kpa)	**Baseline**	**Mean±SD**	20.6±8.3	19.6±9.1	^0.552
		Range	9.5–46.0	9.6–56.0	
	Month-12	**Mean±SD**	13.3±5.4	15.7±7.6	^0.060
		Range	7.0–35.0	7.1–46.0	
	p-value (Intra-groups)		**¤<0.001***	**¤<0.001***	
Fibrosis grades	**Baseline**	**F3**	13 (24.5%)	15 (27.3%)	#0745
		F4	40 (75.5%)	40 (72.7%)	
	Month-12	**F2**	15 (28.3%)	8 (14.5%)	#0.088
		F3	14 (26.4%)	11 (20.0%)	
		F4	24 (45.3%)	36 (65.5%)	
	p-value (Intra-groups)		**§<0.001***	**§0.007***	

Discussion

Our study reports the effect of losartan on the vascular, hepatic, renal and hematological profile of patients with Advanced liver Fibrosis displaying sustained virological Response after Direct Acting Antivirals treatment. As expected and owing to the blood pressure-lowering effect of

losartan, our results exhibited a significant reduction in diastolic and systolic blood pressure at the end of the investigation in the losartan group over the control group. This was consistent with Chang **Meng et al (5)** study, a meta-analysis of randomized

In a controlled trial that assessed the effects of losartan on patients with NAFLD, results showed a decrease in systolic blood pressure to a certain extent **(5)**. In addition, A. W. Schneider reported a significant decrease in mean arterial pressure compared to baseline in the losartan-treated group **(6)**.

Surprisingly, the platelet count significantly increased in the losartan-treated patients, which contrasts with earlier investigations by **Salama et al. and Silvia et al.,** where there was an insignificant alteration in the platelet count of the treated groups **(6, 7)**. This may be explained by the portal venous pressure-lowering effect of losartan, as illustrated in the De **BK et al.** study **(8)**.

Importantly, the mean baseline ALT and AST of our cohort were within the normal range, indicative of the absence of active inflammation after HCV treatment. This contrasts with the studies performed by **Salama et al. and Silvia et al.,** where the mean baseline ALT and AST were highly suggestive of active HCV. Differences in the baseline disease parameters significantly influence the outcome of clinical trials, which may partly explain the above discrepancy **(6, 7).**

Both ALT and AST significantly decreased at 12 months in both treated and control groups; nevertheless, insignificant variance has been observed among both groups, which may correlate with a tendency toward progressive resolution of inflammation and fibrosis. In fact, our results agree with the meta-analysis of several clinical trials indicating that losartan could decrease the alanine aminotransferase level of nonalcoholic fatty liver disease **(5).** Moreover, we suggest that the liver enzymes decreased in the control group due to the eradication of HCV and the gradual recovery of liver functions. Indeed, **Tamori A et al.** showed that ALT concentrations were significantly reduced in cirrhotic cases with SVR **(9)**.

In addition, regarding synthetic liver functions, there was a significant increase in albumin at the end of the study in the losartan group over the control group. This was consistent with Salama's study **(6)**. This potentially implies a regression of fibrosis along with an improvement in overall liver functions.

Regarding creatinine changes among study groups, creatinine significantly decreased at month 12 in both groups, but insignificant variance among losartan and the control group. We believe Losartan has a direct renoprotective effect, as reported in Costantino, V.V., et al. 2020. Our results disagree with Salama et al study; creatinine was not significantly decreased in the losartan group and was not significantly improved in the control group. In the **Silvia Sookoian study**, creatinine non significantly increased in the losartan group non- significantly reduced in the control group **(6, 7)**. This conflict can go with the safety of losartan regarding renal impairment, as there is no significant difference between losartan and control, so we suggest that further study is recommended to assess the effect of losartan long-term usage on creatinine.

Improved kidney functions in the control group could signify a gradual recovery of renal functions after HCV eradication. According to the findings of **Riccardo Nevola et al.**, it was shown that hepatitis C cases who achieved a sustained virologic response had a significant improvement in renal function. This improvement was characterized by a ten percent decrease in serum creatinine levels and a rise in the estimated glomerular filtration rate. **(10)**.

Regarding HCC development during the study, results showed no statistical significance between the losartan group and the control group. Our results regarding HCC incidence after HCV eradication were comparable to **Nagaoki Y. and his colleagues' study (11)**.

In our study, a significant decline has been observed in the FAB-4 score in the losartan group compared to the control group at month 12. In **Ghoneim S. and his colleagues' study,** a statistically significant drop has been observed in the mean FIB-4 score from baseline to post-SVR **(12). A** significant reduction of Fib4 in the losartan group indicates a regression of fibrosis.

Unfortunately, few clinical investigations have been performed to investigate the anti-fibrotic activity of losartan. This poses difficulties in comparing the treatment outcomes of losartan in our studied cohorts. For example, our results showed no statistical difference between losartan and the control group regarding fibrosis regression, while **Salama et al.** reported losartan inhibitory effects on the progression of liver fibrosis in chronic hepatitis C cases, and statistically significant variance has been observed among losartan and control groups **(6)**. The patients' cohorts were different in the two studies; **Salama et al** study included a smaller number of patients with positive HCV viremia compared to our study, which had a higher number of patients recruited after SVR.

The lack of statistical significance in our study may be attributed to several factors. For example, in the Salama **et al. study**, where significant regression of fibrosis was reported in patients on losartan treatment, fibrosis was histologically assessed by liver biopsy, which is the gold standard for evaluating changes in liver fibrosis. Moreover, our cohort had advanced baseline fibrosis (F3, F4), which, in addition to being in favor of irreversibility, may partly explain the inability of the dose of losartan used for the specified period of time to significantly induce regression of fibrosis **(6)**. Furthermore, **Silvia et al. (7)** studies were carried out during the IFN treatment era of HCV on chronic hepatitis C non-responders with contraindications or a lack of compliance with interferon plus ribavirin therapy. Besides, losartan was given for six months, and fibrosis was assessed by liver biopsy. In addition, the sample size of the study was comparatively smaller, and not all patients displayed advanced fibrosis. Once again, in contrast to our study, the results showed significant regression in fibrosis in the Losartan-treated group compared to controls **(7)**, which may reflect the several differences between the two studies.

Finally, we have not observed serious side effects attributable to losartan administration during the study, which agrees with earlier reports **(7, 6)** and the overall safety of the drug in other vascular and fibrotic disorders.

Conclusion

We concluded that Losartan has an established safety profile in cases of compensated liver cirrhosis, it could promote better outcomes in the early fibrosis stages by improving the synthetic liver functions and platelet counts.

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