International Journal of Advances in Medicine
Toma L et al. Int J Adv Med. 2020 Sep;7(9):1302-1306
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: http://dx.doi.org/10.18203/2349-3933.ijam20203592

Original Research Article

Evolution of arterial hypertension in patients with hepatitis C virus cirrhosis after antiviral treatment

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Received: 06 July 2020
Accepted: 04 August 2020

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ABSTRACT

Background: Chronic hepatitis C (HCV) infection has direct and indirect manifestations that promote vascular resistance. On the other hand, HCV infection leads to liver cirrhosis and complications such as cardiomyopathy, characterized by a hyperdynamic state with low peripheral vascular resistance. The aim of this paper is to study the evolution of arterial hypertension in patients with liver cirrhosis, after the cure of HCV infection.
Methods: This is a prospective observational cohort study including 261 hypertensive patients with compensated HCV cirrhosis who underwent direct-acting antiviral treatment. Blood pressure was monitored at the initiation of antiviral therapy and at 3, 6 and 12 months follow-up. Screening for cirrhosis complications was performed and patients were also monitored by electrocardiography, liver and kidney function tests, serum lipids and N-terminal pro-B-type natriuretic peptide.
Results: Virologic response after antiviral treatment led to a better control of arterial hypertension with a decrease of 24 hours mean blood pressure by 15% (p=0.04, CI 95%). In patients with stable liver disease serum levels of N-terminal pro-B-type natriuretic peptide slowly decreased at 6 and 12 months (p=0.02, p=0.03), while in patients with cirrhosis decompensation the levels increased. Also, patients with decompensated cirrhosis presented lower blood pressure values and required discontinuation of antihypertensive drugs.
Conclusions: Curing HCV infection may lead to a better control of blood pressure in patients with compensated liver disease. However, an abrupt decrease in blood pressure may be a clinical sign of progressive liver disease and cirrhotic cardiomyopathy.

Keywords: Arterial hypertension, Cirrhotic cardiomyopathy, HCV infection, Liver cirrhosis,

INTRODUCTION

Arterial hypertension is one of the most common pathologies worldwide, with an estimated prevalence of 30-45%.[1] A continuous relationship between high blood pressure and acute cardiovascular events (myocardial infarction, stroke) as well as end-stage kidney disease in well acknowledged.[2] However, hypertension- mediated organ damage, even in subclinical forms, has been associated with chronic conditions such as atrial fibrillation, heart failure, dementia, chronic kidney disease and its complications, with important implications in morbidity and quality of life.[2] Essential hypertension is caused by an association of genetic, environmental and behavioral factors.[3] One of the key factors in the development of hypertension is considered

to be the chronic high salt intake, as well as an increased sympathetic activity. On the other hand, microvascular dysfunction (classically described in type 2 diabetes mellitus) may lead to increased peripheral vascular resistance, which in turn acts as a precursor for arterial hypertension.[4,5]

Chronic hepatitis C (HCV) currently affects 71 million individuals worldwide, thus being one of the most frequent causes of liver disease, along alcoholic liver disease, non alcoholic steato-hepatitis and chronic hepatitis B infection.[6] Besides liver damage, the HCV virus has a series of extra-hepatic manifestations, including cryoglobulinemic vasculitis, lymphoma, type 2 diabetes mellitus and also cardiovascular disorders.[7,8] Due to a proinflammatory state involving primarily tumor necrosis factor alpha, HCV promotes hepatic and systemic insulin resistance and contributes to the development of diabetes mellitus in chronically infected patients.[9] As shown above, this may lead to increased peripheral resistance and arterial hypertension. Furthermore, HCV infection has been associated with the production of carotid artery plaques and coronary heart disease, as well as an increased risk for death caused by coronary artery disease proportional to the serum values of HCV- RNA.[7] Also, HCV cure reduces the cumulative incidence of death, end-stage renal disease, ischemic stroke and acute coronary syndromes.[10]

The natural evolution of HCV infection leads to liver cirrhosis and end-stage liver disease. This is characterized by a series of pathophysiologic processes and the development of portal hypertension and liver failure, with complications such as jaundice, coagulopathies, esophageal varices, ascites, hepato-renal syndrome and cirrhotic cardiomyopathy (CCM).[11] This is defined as an impaired contractile response to stress and an impaired diastolic function, frequently associated with electrophysiological changes. The result is a hyperdynamic circulation with decreased peripheral resistance. The presence of CCM has an impact on overall survival of cirrhotic patients both before and after liver transplantation.[12] Current guidelines establish the diagnosis of CCM based on echocardiographic criteria; however, electrocardiographic patterns and increases in brain natriuretic peptide are important in supporting the diagnosis.[13,14] As a result, patients which were hypertensive may become normotensive or hypotensive in the natural history of the liver disease.

The aim of this paper is to describe the evolution of arterial hypertension following HCV cure in cirrhotic patients. The hypothesis of the study is that HCV cure may reduce the systemic proinflammatory state and may decrease peripheral vascular resistance, leading to lower blood pressure values in hypertensive patients. On the other hand, a major decrease in blood pressure may indicate a progression of the liver disease.

METHODS

We performed a prospective observational study including 261 patients with a history of arterial hypertension and HCV cirrhosis, admitted to our clinic from December 2015 to July 2018. The patients were selected from the pool of patients treated in the National Healthcare Program for HCV infection.[15] All the patients had genotype 1b HCV and received direct acting antiviral treatment with ombitasvir, paritaprevir, ritonavir and dasabuvir for a duration of 12 weeks, according to treatment protocol. Sustained virologic response was confirmed by undetectable HCV-RNA 12 weeks after the end of treatment.

Exclusion criteria were co-infection with HIV or HBV, other causes of liver disease such as alcohol abuse or autoimmune disorders, history of liver decompensation (either cirrhosis complication or Child Pugh Class B or C), secondary arterial hypertension, end-stage kidney disease, presence of hepatocellular carcinoma or other malignancies.

The diagnosis of HCV cirrhosis was based on the presence of detectable plasma HCV-RNA and non-invasive estimation of fibrosis either by Fibromax® or Fibroscan®, as well as ultrasonography aspect of the liver and signs of portal hypertension.

Patients were evaluated at the initiation of antiviral therapy, at the end of therapy (3 months), at 6 months (when virologic response was also assessed) and at 12 months. The patients were divided into 2 groups during follow-up: those who maintained a stable liver disease and those who presented cirrhosis decompensation. Follow-up visits included ambulatory blood pressure monitoring (ABPM) over 24 hours, using 24 h mean value, day-time mean blood pressure and night-time mean blood pressure as variables. Also, current antihypertensive medication and doses were noted. An electrocardiography was performed at each visit and QT interval was recorded.

Laboratory parameters monitored were liver function tests, kidney function tests, blood cell count, coagulation parameters, serum cholesterol, and N-terminal pro-B-type natriuretic peptide (NTproBNP).

The study was approved by the local Ethical Committee. All the patients signed an informed consent form. Statistical analysis was performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Numerical variables were expressed as mean±standard deviation. The ANOVA test was used for group comparison, with statistically significant p values of less than 0.05.

RESULTS

The majority of patients in the study cohort were female (60.53%), with a mean age in the cohort of 56.32±13.28

years. None of patients presented significant liver cytolysis at baseline. Mean total bilirubin and international normalized ratio (INR) were within normal limits, as expected in a cohort of patients with compensated cirrhosis. 24h mean systolic blood pressure (sBP) was increased with a mean of 138±15 mmHg, as well as 24h mean diastolic BP (dBP)- 79±13 mmHg. There was a clear difference between daytime and night time BP (sBP of 142±14 mmHg versus 133±10 mmHg p=0.04 and dBP 84±6 mmHg versus 73±12 mmHg, p=0.03 respectively). Patients were using angiotensin converting enzyme inhibitors (ACEi) or sartans (ARB) (71.64%), diuretics- including mineralocorticoid receptor antagonists (47.89%), beta-blockers (35.63%), calcium channel blockers (28.73%) and alpha-blockers (18.39%). Most of the patients were under treatment with two or more antihypertensive drugs (80.07%). At initiation of antiviral therapy, patients receiving calcium channel discontinued treatment due to drug-to drug interactions and were given ACEi or ARB; the rest of the patients continued the same treatment and only reinforcement of dietary measures was performed. Mean QT interval duration was within normal limits (413±18 ms), while NTproBNP levels were slightly increased (234±118 pg/ml). All the patients achieved sustained virologic response.

Table 1: Baseline characteristics and evolution of patients without cirrhosis decompensation (n=239).

No. of patients	Baseline	3 months	6 months	1 year	P value
Gender (male/female)	103/136				
Mean age	55.27±17.2				
ALT (IU/ml)	42 ±23	37+/19	38±15	35+/17	0.67
AST (IU/ml)	39±14	41±21	35±18	36±12	0.43
Total Bilirubin (mg/dl)	0.7±0.5	0.8±0.3	0.7±0.4	0.8±0.4	0.38
Albumin (g/dl)	4.3 ±0.7	4.1±0.5	4.2±0.5	4.4±0.5	0.61
INR	0.9±0.10	1.0 ±0.13	1.03±0.09	0.9±0.05	0.57
Creatinine (mg/dl)	0.7±0.5	0.8±0.5	0.8±0.4	0.7±0.5	0.46
QT (ms)	416±17	421±19	419 ±15	421±18	0.59
24h mean sBP (mmHg)	138±12	125±8	110±12	116±7	0.01
24h mean dBP (mmHg)	78±12	73±8	70±9	67±7	0.03
Daytime mean sBP (mmHg)	142±13	138±10	135±4	130±7	0.03
Daytime mean dBP (mmHg)	84±7	81±6	79±6	70±7	0.02
Nighttime mean sBP (mmHg)	132±10	129±7	121±5	110±5	0.001
Nighttime mean dBP (mmHg)	73±12	70±8	64±5	63±4	0.04
NTproBNP (pg/ml)	231±119	218±96	203±82	186±85	0.03
Number of patients using 2 or more antihypertensive drugs	203	175	156	132	0.001
Number of patients requiring dose reduction of antihypertensive medication	-	57	23	48	0.05

Table 2: Evolution of BP, NTproBNP and QT interval in patients with cirrhosis decompensation (n=22).

No. of patients	Baseline	3 months	6 months	1 year	P value
Gender (male/female)	10/12				
Mean age	56.89±10.32				
QT (ms)	418±15	432±21	436 ±13	439±15	0.05
24h mean sBP (mmHg)	137±15	130±10	124±8	103±11	0.04
24h mean dBP (mmHg)	77±13	70±11	63±5	60±6	0.001
Daytime mean sBP (mmHg)	141+/15	131±8	124±9	113±6	0.001
Daytime mean dBP (mmHg)	85±7	77±8	69±4	62±5	0.001
Nighttime mean sBP (mmHg)	133±8	128±11	123±7	98±6	0.001
Nighttime mean dBP (mmHg)	76±11	61±9	66±4	58±7	0.02
NTproBNP (pg/ml)	228±124	262±110	329±75	438±97	0.01
Number of patients using 2 or more antihypertensive drugs	13	5	3	1	0.001
Number of patients requiring dose reduction of antihypertensive medication	-	22	13	9	0.05

At follow-up, most patients (91.6%) presented preserved liver function and compensated cirrhosis. Table 1 presents the characteristics and evolution of this group of patients.

During the 1 year follow-up, 22 patients (8.4%) presented decompensation of liver disease: 3 patients presented upper gastrointestinal bleeding from esophageal varices, 10 patients developed ascites (one also developed spontaneous bacterial peritonitis and hepatorenal syndrome), 4 patients developed hepatorenal syndrome and 5 patients developed sings of liver failure with jaundice and hypoalbuminemia.

Since the number of patients is much smaller than that of patients with stable liver disease, a comparison between study groups is not significant. Furthermore, the type of decompensation varied greatly therefore the evolution of biological parameters reflecting liver status is irrelevant. However, in this small group of patients, statistically significant information has been obtained regarding evolution of BP and BP treatment (Table 2).

Interestingly, while in the compensated cirrhosis group patients-maintained differences between night and day BP, in the decompensated cirrhosis group these differences were insignificant (p=0.03 versus p=0.27, 95% CI). Moreover, patients with decompensated cirrhosis had a more significant reduction in BP values at one year follow up (15.32% in the compensated cirrhosis group versus 24.81% in the decompensated cirrhosis group, p=0.04). More patients with episodes of decompensation required antihypertensive drug discontinuation or dose decrease. The increase in NTproBNP as well as the prolongation of QT interval suggests that patients with cirrhosis decompensation also developed cirrhotic cardiomyopathy.

DISCUSSION

The decrease of blood pressure after the onset of cirrhosis is commonly described in literature.[16,17] The typical aspect is of low blood pressure in morning with night-time normalization, probably due to abnormal regulation of BP.[18] The anomalies in regulatory systems as well as the diurnal variation of BP are supposed to have an important contribution in the water and salt retention in cirrhosis. Studies also show that the progression of hemodynamic abnormalities is proportional to the progression of liver disease.[19] This is consistent with the data from our study, which emphasizes the decrease in BP in patients with cirrhosis decompensation.

However, HCV patients have particular mechanisms involved in cardiovascular regulation. It is clear that HCV infection is associated with increased arterial stiffness, by two main pathways.[20] First, HCV infection promotes non-alcoholic fatty liver disease, which creates a pro-inflammatory state and associates increased arterial stiffness; secondly, HCV itself is linked independently to arterial stiffness. The current supposition is that inflammation induced by HCV cannot be characterized by general markers (such as C-reactive protein) and requires determination of more specific serologic markers (such as interleukins). The study aforementioned also proves a direct relationship between HCV chronic infection and increased BP. Our research suggests that that HCV cure in cirrhosis patients is associated with a better control of BP values, and with a reduction in antihypertensive medication.

Chronic HCV hepatitis is also associated with cardiac remodeling in the absence of cirrhosis and cirrhotic cardiomyopathy.[21] HCV cure results in a decrease in left atrial volume, left ventricular mass, indexed right atrial volume, pulmonary pressure and vena cava diameter. These findings underline the importance of viral infection itself in cardiovascular pathophysiological processes, apart from the current definition of cirrhotic cardiomyopathy, which may appear in cirrhosis regardless of etiology. Another study suggests that HCV clearance is associated with a reduction in cardiovascular events of 2-3.5 folds in the setting of direct acting antiviral treatment, independent of degree of fibrosis or choice of treatment.[22]

CONCLUSION

The link between arterial hypertension and HCV infection is based on the systemic inflammation associated with the viral infection leading to increased arterial stiffness as well as cardiac re-modelling. HCV cure results in better control of BP and a decrease in cardiovascular risk. On the other hand, decompensation of liver disease is associated with dramatic decreases in BP and these may represent important clinical markers in suspecting a progression of liver failure.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee of Fundeni Clinical Institute, Bucharest, Romania

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Cite this article as: Toma L, Mercan-Stanciu A, Zgura A, Bacalbasa N, Diaconu C, Iliescu L. Evolution of arterial hypertension in patients with hepatitis C virus cirrhosis after antiviral treatment. Int J Adv Med 2020;7:1302-6.