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Evaluation of liver fibrosis and carotid intima-media thickness index (C-IMT) in patients with chronic hepatitis C virus before and after direct-acting antiviral treatment (DAA)

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ABSTRACT

Introduction. Viral hepatitis is still a challenge for the medical world and research over the past decades has been aimed at discovering viable methods of prevention, diagnosis and treatment.
Material and methods. Data analysed from 73 patients from "Dr. Victor Babeș" Clinical Hospital of Infectious and Tropical Diseases and "Dr. Victor Babeș" Private Medical Clinic, both from Bucharest.
Results. Fibroscan assessment showed that patients predominantly have F2, F3, F4 Metavir fibrosis stage while FibroTest showed F3, F4 stage of fibrosis. It was observed a decrease in fibrosis stage after DAA treatment comparative to values before treatment (5.622 kPa average post-treatment comparative to 11.49 kPa before treatment, statistically significant with p value <0.001). Chronic infection with hepatitis C virus is considered a risk factor for atherosclerosis correlated with a higher cardiovascular risk compared to the general population. Monitoring patients prior to and after DAA treatment is an efficient method to detect early vascular changes that could lead to thrombotic and/or cardiovascular events.
Conclusions. Measurement of the IMT index by doppler ultrasound in patients with hepatitis C virus infection may constitute a method of identification the endothelial dysfunction or atherosclerosis and may help to establish cardiovascular risk. Elimination of hepatitis C virus is the target of ongoing international programmes but the extrahepatic effects of persistent infection, early diagnosis and appropriate treatment should not be neglected.

Keywords: hepatitis, virus C, IMT, cardiovascular, extrahepatic, DAA

Abbreviations
DAA: direct-acting antivirals
CCA: common carotid artery
CCA-IMT index: common carotid artery-intima-media thickness
WHO: World Health Organization
HCV: hepatitis C virus
SVR: sustained virologic response

INTRODUCTION

Viral hepatitis is still a challenge for the medical world and research over the past decades has been aimed at discovering viable methods of prevention, diagnosis and treatment [1]. In 2020, in a pandemic year due to SARS-CoV-2 infection, the Nobel Prize for Medicine was granted to researchers who in the 1970's began research on hepatitis C virus that led to

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confirmation of its existence in 1989, opening the way to diagnosis and treatment of this pathology [2].

The effects of chronic infection are not only located on the liver, but also affect the entire body, causing so called extrahepatic manifestations such as skin, neurological, vascular, metabolism [2,3]. Treatment of hepatitis C chronic infection as well as monitoring extrahepatic manifestations but also assessing the quality of life of these patients are important premises in the fight to reduce the incidence of this pathology and also limiting systemic effects [3].

OBJECTIVES

This study aims to assess the degree of liver fibrosis and the carotid-intima media thickness (C-IMT) in patients with hepatitis C virus (HCV) treated with direct-acting antivirals (DAA).

MATERIALS AND METHODS

We made a prospective study in the period November 2018-January 2020. Data were analysed from 73 patients from Clinical Hospital of Infectious and Tropical Diseases ”Dr. Victor Babeș”, Bucharest and ”Dr. Victor Babeș” Private Medical Clinic. The analysis was a preliminary one, an ”intra-subject” analysis. The final analysis will include a number of 105 patients. Inclusion criteria: liver fibrosis F1-F4 Metavir, naive or previously treated with Interferon. Exclusion criteria: decompensated liver cirrhosis (Child-Pugh >6 points or complications), liver cancer without therapeutic indication, extrahepatic malignacies not receiving curative treatment, hepatitis B virus co-infection, HIV co-infection. Patients were evaluated before DAA treatment and 3 months after completion of therapy. Liver fibrosis was evaluated by Fibroscan at the ”Dr. Victor Babeș” Private Medical Clinic and IMT was evaluated by doppler ultrasound in the common carotid arteries (CCA). Patients expressed their agreement to participate in the study signing and informed data processing consent. The study was approved by the Ethics Committee of ”Dr. Victor Babeș” Clinical Hospital.

The data were statistically analyzed using SPSS software (Spearman-rho correlation, Pearson-r, t-Student test, Kendall-tau) and Microsoft Excel.

RESULTS

Results from 73 patients have been analyzed before DAA treatment and 3 months after the treatment.

Depending on the gender, the predominance of females was observed. Among the analyzed patients, most of them (54 patients) were in the age range 50-80 years-old (figure 1), most of them living in the urban area (60 patients), levels of education was predominantly medium (53 patients).

From the analyzed group, liver stage of fibrosis was predominantly F2 and F3 Metavir. There were 2 patients with excess fat tissue that did not allow examination by Fibroscan and they were only assessed by Fibromax. Before starting DAA treatment, 6 patients had Fibroscan values corresponding to decom-

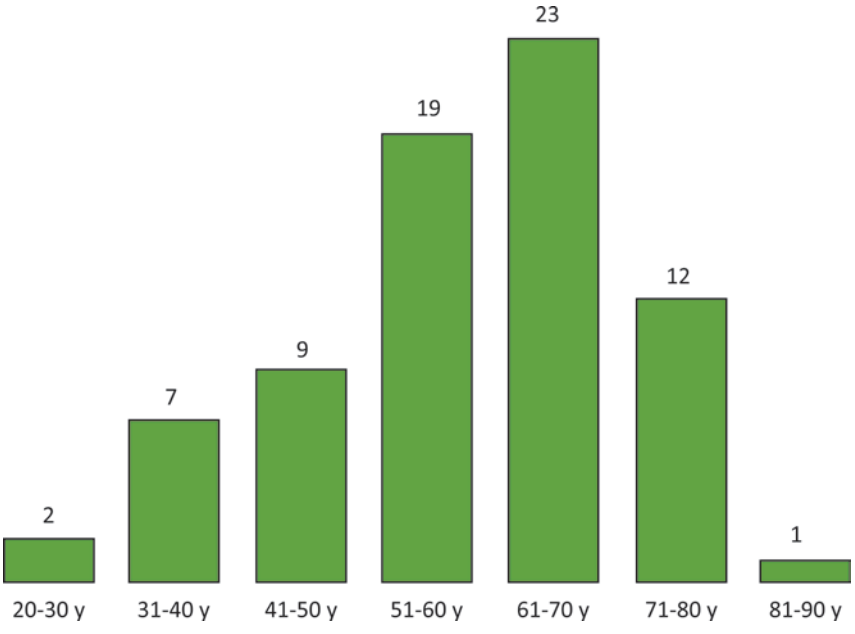

FIGURE 1. *Age distribution of the patients*

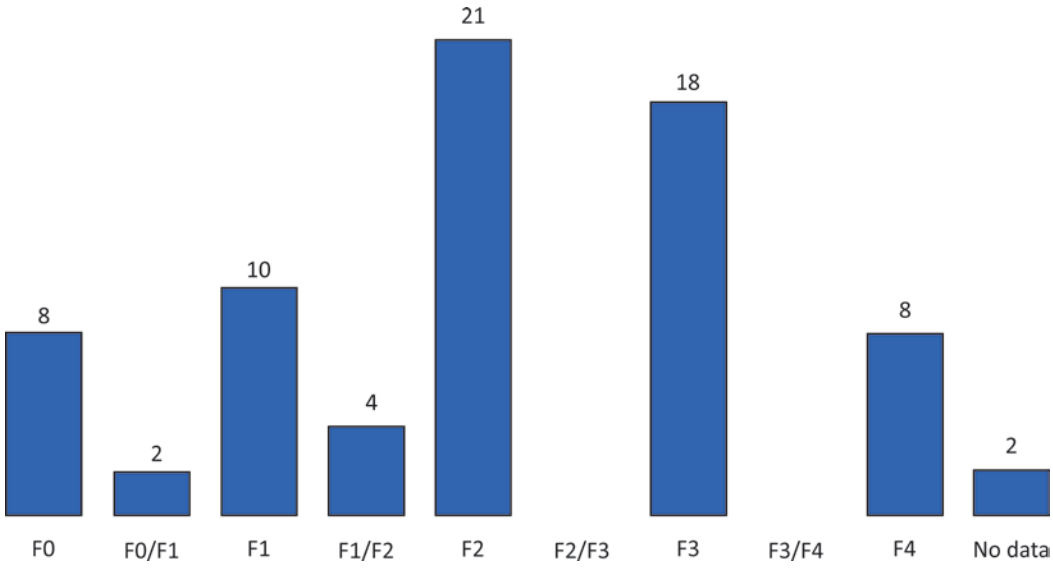

FIGURE 2. *Liver fibrosis evaluated by Fibroscan before using DAA treatment*

pensated liver cirrhosis. Patients with these values were further investigated and assessed gastroenterologically. All the patients had sustained virological response (SVR) after DAA treatment.

It was observed a decrease in liver fibrosis stage after DAA treatment comparative to values before treatment (5.622 kPa average post-treatment comparative to 11.49 kPa before treatment), statistically significant with p value <0.001.

Doppler ultrasound image of a 55-year-old patient with CCA-IMT index value over 0.80 mm. Three measurements were used: two performed on the distal wall and one on the proximal wall of the CCA.

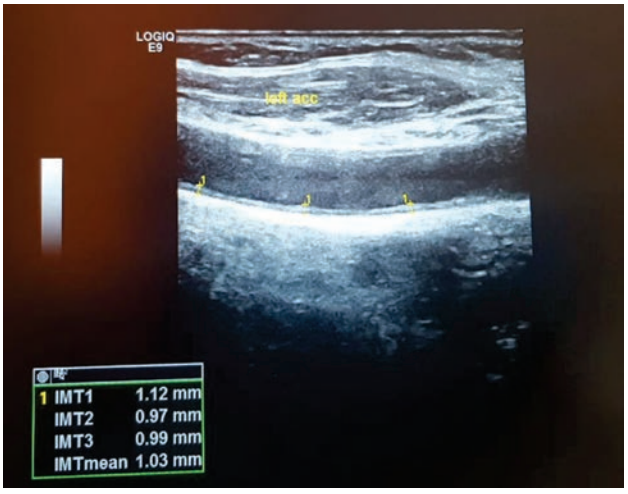

FIGURE 4. *Doppler ultrasound examination with CCA-IMT index*

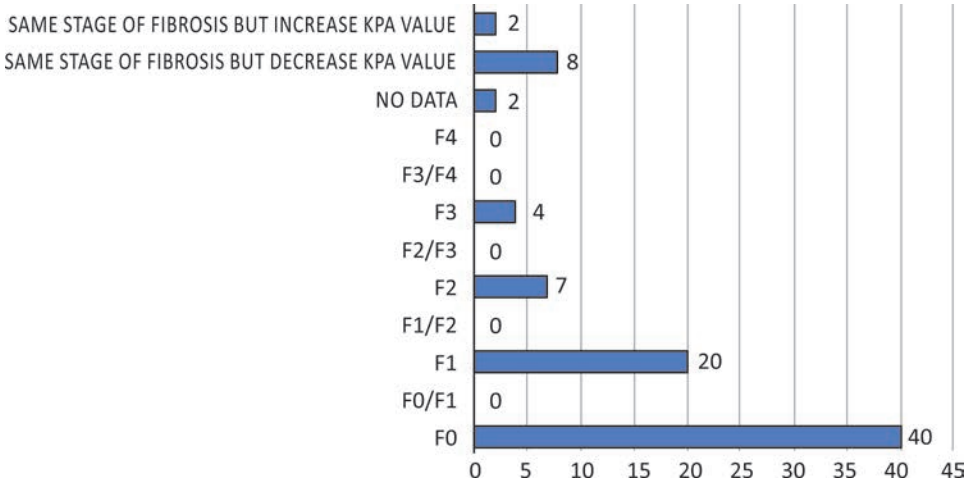

FIGURE 3. *Liver fibrosis evaluated by Fibroscan after using DAA treatment*

DISCUSSION

Fibroscan is an easy method, non-invasive device that assesses the liver stiffness using the technique of transient elastography [5]. It measures the elasticity of a volume equivalent to a cylinder of 1 cm diameter and 4 cm length representing approximately 1/500 of the liver volume, the surface is at least 100 times higher than the area analysed during the liver biopsy [5]. The results are presented in kilopascali (kPa) and correspond to the median value of 10 valid measurements. The determined values are between 2.5 and 75 kPa [5].

Fibroscan and Fibrotest correlations (Kendall-tau, Spearman-rho) before treatment were statistically significant with p value = 0.001. The same data was observed in a study published by Cheng et al., who revealed a decrease in liver fibrosis after DAA treatment and also laboratory improvement of the aspartate aminotransferase and platelet ratio index [15].

The most frequently comorbidities associate are hypertension, dyslipidemia and diabetes mellitus treated with hypoglycaemic agents. Literature said that around 30-40% from the patients with persistent infection develop extrahepatic manifestations, such as: lymphoma, cryoglobulinemia, glomerulonephritis, porphyria cutanea tarda, insulin-resistance, diabetes, Sjögren's syndrome, vascular disease (cardiovascular, cerebrovascular) [8].

In analysed group was observed a decrease in blood sugar levels after DAA treatment, without any modifications in diabetes medication. The mean blood sugar level decreased after DAA treatment compared to the mean prior to starting the DAA's with p value = 0.003 (98.58 pre-treatment average compared to 91.26 post-treatment). It is important to evaluate patients to see how long is this effect of DAA therapy on metabolic changes. Similar data was published by Weidner et al. in a retrospective study from 2018. The study evaluated 281 patients treated with DAA and revealed that successful HCV treatment may have an impact in reducing glucose level, pre-diabetes, the need of treatment for diabetes, and ultimately diabetes-associated morbidity [9]. This metabolic change was BMI-independent [9]. Different other studies suggest that there is an improvement on insulin sensitivity in diabetic and non-diabetic patients with HCV receiving DAA treatment [10,11]. Moreover, glucose metabolism parameters of HCV infected patients improve early after DAA treatment, with benefits that are not limited to diabetics. Viral eradication was associated with a significant reduction in blood glucose levels and fasting insulin in both groups (F0-F2 and F3-F4) at the end of treatment. The significant reduction was maintained after 24 weeks of posttreatment follow-up [11,12].

These findings confirm how deep and widespread are the effects exerted by HCV infection [10,11].

In our study, body-mass index (BMI) was range between 16.8 and 38.2 cm^2/kg and 29 patients were overweight. It was observed a statistically significant correlation between patient weight (BMI) and severe fibrosis stages before DAA treatment with p value = 0.009. The same results were obtained in different studies evaluating Egyptian population with HCV. Is well known that Egypt has the highest HCV prevalence worldwide [13]. They showed that it is a significant association between severe liver fibrosis and obesity [13,14]. In the analysis of the study, BMI, albumin, alfa-fetoprotein were designated as significant predictors associated with the severe fibrosis in HCV Egyptian patients [13,14].

C-IMT is a highly reproducible and non-invasive parameter for assessing the atherosclerotic process. Regarding the evaluation by doppler ultrasound, the measurement on the proximal wall is not so often used in the standard assessment (according to Mannheim Consensus) but is more sensitive in identifying pathological changes in vascular disease thus increased IMT correlates more to cardiovascular risk than cerebrovascular [2]. Pathological values: below 60 years IMT value >0.80 mm.

Were analysed 30 patients by doppler ultrasound, age range between 30 to 75 years old. As associated comorbidities they had cardiovascular diseases, diabetes mellitus and dyslipidemia. The stage of fibrosis was predominantly F2-F3. The BMI was between 22,5-37 kg/m^2. DAA treatment used: ledispavir/sofosbuvir, ombitasvir/paritaprevir/ritonavir, grazoprevir/elbasvir depending on age, needs and comorbidities of each patient. The duration of the treatment was 12 weeks in 58 patients. Doppler assessment could not be made in all 73 patients because some of them did not want to be examined.

Chronic infection with hepatitis C virus is considered a risk factor for atherosclerosis correlated with a higher cardiovascular risk compared to the general population [3]. Monitoring patients prior to and after DAA treatment is an efficient method to detect early vascular changes that could lead to thrombotic and/or

cardiovascular events [4]. Patients analised already have predisposing factors for the development of clogged arteries (hypertension, diabetes mellitus, dyslipidemia) and the hepatitis C virus infection is an additional element that might increase the risk for atherosclerosis process [4].

An important aspect of the study is that none of the patient were treated (nor started treatment during the DAA administration) with hypolipemiant medication such as statins, fibrates or other compounds. The purpose of our study was to see if the DAA treatment changes (increase or decrease) the IMT index or reduces size of pre-existing carotid plaques. From 30 analysed patients, 23 showed a decrease in CCA-IMT index on the right carotid artery and 27 a decrease in CCA-IMT index on the left carotid artery; 6 patients did not have any changes and 1 patient had an increased CCA-IMT after treatment. Even though the CCA-IMT index values were not above the normal limit, their decrease during treatment with DAA is an argument on the use of this therapy to limit some extrahepatic effects of the disease.

Beyond conventional risk factors involved in atherosclerotic pathology, the role of systemic inflammation in the genesis of atherosclerosis is increasingly studied. Various studies suggest an increased risk of atherosclerosis evaluated by measuring the IMT index in patients with HCV [4]. A study published in 2020 and assessing the risk of atherosclerosis in HCV patients suggests that HCV is an independent risk factor for atherosclerosis increasing the risk of developing cardiovascular and neurological events by increasing oxidative stress, proinflammatory cytokines production and endothelial dysfunction [7]. The study analysed a group of 24 patients before and after DAA treatment and the results showed that there was a decrease in CCA-IMT and also the inflammatory markers, but there is a need to increase the sample size to define whether there is a decrease in cardiovascular risk [7]. A multicenter study has shown that the eradication of HCV by DAA has led to an improvement in carotid atherosclerosis and in particular a significant reduction of the IMT [17]. It is also important to take into consideration that in patients with advanced atherosclerosis, as evidenced by the presence of carotid plaques, the clearance of HCV did not lead to significant changes in plaque value [17]. It has been reported that atherosclerosis in HCV patents was also associated with advanced liver fibrosis [17]. Other studies suggest that HCV clearance improved not only liver function, but also endothelial dysfunction and subclinical atherosclerosis [16,17].

Multiple studies strongly suggest that HCV is an independent, risk factor for cardiovascular diseases [16]. Evidently DAA treatment and SVR achievement reduces cardiovascular risk [18,19]. In addition, eradication of HCV with DAA results in notable amelioration of endothelial function in patients with chronic hepatitis [18-20]. It is most probable that DAA treatment will reduce the prevalence of cardiovascular events in patients with chronic hepatitis C [18-20], but further research is needed to evaluate the long-term effects of that.

All HCV patients should be evaluated from the beginning of diagnosis (if is possible) to identify early signs of endothelial dysfunction and initiate the right treatment to pevent atheroslcerosis process [4].

In the context of SARS-CoV-2 pandemic, monitoring these patients was much more difficult and their compliance has decreased. Regardless of the epidemiological context, we must not forget that hepatitis C virus is still a public health issue with real effects on morbidity and mortality [6]. In this pandemic year, the targets of international programmes organised by World Health Organization on prevention, diagnosis and treatment of viral hepatitis have been slowed, their performance has been altered [6].

As regards the ongoing study, the subject is one of interest, therefore is it necessary to continue monitoring and extension of the group of patients for the full analysis of the DAA effects on the IMT index and also the possibility in contouring new therapeutic strategies relating to atherosclerosis, especially in HCV patients.

CONCLUSIONS

DAA treatments are a therapeutic innovation that has given effective results in healing chronic hepatitis C virus infection, but the extrahepatic effects of persistent infection, early diagnosis and appropriate treatment should not be neglected. Measurement of the IMT index by Doppler ultrasound in patients with hepatitis C virus infection may constitute a method of identification the endothelial dysfunction or atherosclerosis and may help to establish cardiovascular risk. Extrahepatic manifestations of hepatitis C virus would be a challenge for the medical world because the effects will be observed for a long time even if the chronic infection was cured.

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