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ORIGINAL ARTICLE

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Myocardial perfusion reserve in patients with chronic hepatitis C before and after direct-acting antiviral treatment—a pilot study

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Abstract

Introduction: Patients with chronic hepatitis C (CHC) have an increased risk of atherosclerotic cardiovascular disease which may be due to inflammation and endothelial dysfunction caused by the chronic infection. In this prospective pilot study, we assessed, for the first time among patients with CHC the myocardial perfusion reserve (MPR) by Rubidium-82 (^{82}Rb) positron emission tomography (PET)/computed tomography (CT) before and after direct-acting antiviral (DAA) treatment and compared them with biomarkers of systemic inflammation and endothelial dysfunction.

Methods: We included 10 patients with CHC who received 8 or 12 weeks of DAA treatment. To obtain the MPR, a cardiac ^{82}Rb PET/CT scan at rest and adenosine-induced stress was performed at baseline and between 12 and 24 weeks post DAA treatment. Additionally, markers of endothelial dysfunction and inflammation were measured at baseline and 12 weeks after DAA treatment.

Results: All 10 patients achieved cure and the median age was 50 (range: 40–62 years). The median MPR before treatment was 3.1 (range: 2.3–4.8) compared to 2.9 (range: 2.2–4.1) after DAA treatment $p = 0.63$. Also, cure after DAA treatment was not associated with an overall significant decrease in markers of endothelial dysfunction and inflammation.

Discussion: Cure after DAA treatment in patients with CHC did not improve coronary microvascular function nor did it lead to a decrease in soluble markers of cardiovascular risk in the given time frame where the patients were followed. It should be noted, that MPR before DAA treatment was in the normal range. Considering the small sample size and short follow-up time, further studies are warranted to determine if viral clearance has an effect on coronary microvascular function and endothelial dysfunction.

KEYWORDS

^{82}Rb PET/CT, ^{82}Rubidium positron emission tomography/computed tomography, DAA treatment, endothelial markers, hepatitis C virus, MPR

1 | INTRODUCTION

Hepatitis C Virus (HCV) is one of the leading causes of liver disease-related morbidity and mortality worldwide (Lombardi & Mondelli, 2019). The approval of several direct-acting antiviral (DAA) regimens in recent years has revolutionized the treatment of chronic hepatitis C (CHC) with cure rates, defined as undetectable HCV-RNA 12 weeks after DAA treatment completion (=sustained virologic response [SVR]) > 90% in treated patients (Manns et al., 2017). CHC causes progressive liver damage which might result in liver cirrhosis and hepatocellular carcinoma, but has also been associated with an increased risk of cardiovascular disease (CVD) (Roed et al., 2012). Several biological mechanisms have been suggested to explain the relation between CHC and CVD where steatosis in the liver causes upregulation of inflammatory biomarkers which cause deposits of fatty acids in the arterial wall that can lead to thickening of the artery walls and promote the development of atheromatous plaques as well as viremia may have a pro-inflammatory effect that can enhance the atherosclerotic process (Muñoz-Hernández et al., 2020; Rafieian-Kopaei et al., 2014; Roed et al., 2014). It has also been shown that HCV can colonize and replicate within carotid plaques which can cause inflammation leading to stiffness of the artery wall (Boddi et al., 2010; Muñoz-Hernández et al., 2020).

Coronary microvascular dysfunction is thought to reflect the early changes that occur in the progression towards coronary artery disease (Camici & Crea, 2007). Dynamic positron emission tomography (PET)/computerized tomography (CT) imaging using ^{82}Rubidium (^{82}Rb) as perfusion tracer during stress and rest allows for the quantification of the myocardial perfusion reserve (MPR), which is the vasodilator function of the coronary circulation. MPR quantified by PET/CT has proven sensitive and highly predictive of future CVD in the general population (Murthy et al., 2011; Ziadi et al., 2011).

The present study was conducted as a prospective pilot study and our hypothesis was that patients with CHC, who are cured after DAA treatment, experience an improvement in suspected HCV-induced inflammation and cardiovascular endothelial dysfunction. Therefore, for the first time in patients with CHC, we describe the MPR assessed by ^{82}Rb PET/CT and levels of biomarkers related to endothelial dysfunction before and after DAA treatment.

2 | METHODS

2.1 | Participants

The study was conducted as a pilot project and patients with CHC, who initiated DAA treatment± ribavirin (RBV) between 1 August 2016 and 1 March 2018 were recruited from the Department of Infectious Diseases, Copenhagen University Hospital, Hvidovre. Eligible patients were 18–70 years and registered with CHC, genotype (GT) 1 or 3 in the Danish Database for Hepatitis B and C (DANHEP) (Hansen et al., 2009). The patients had to fulfil the national treatment criteria defined as: liver biopsy (Metavir score ≥ F2), transient elastography (TE) ≥ 10 kPa (Bedossa & Poynard, 1996), clinical cirrhosis or clinically important extra-hepatic manifestations (porphyria cutanea tarda, glomerulonephritis, arthritis, severe debilitating fatigue, neuropathy caused by cryoglublinemia, women of childbearing age with a fertility wish, specific types of B-lymphoma, severe skin disorders and vasculitis). According to national treatment guidelines, cirrhosis was defined as a liver biopsy with a Metavir score of F4 and/or a median elasticity at TE of ≥17 kPa (Christiansen et al., 2014). Exclusion criteria were severe uncontrolled asthma, pregnancy, coinfection with HIV or hepatitis B virus, decompensated cirrhosis (Child-Pugh B and C), or hepatocellular carcinoma.

For two patients, the results of their DAA treatment have previously been described (Sølund et al., 2018).

2.2 | Ethical statement

This study complied with the declaration of Helsinki and all patients received oral and written information and gave written consent before inclusion. The study was approved by the Danish Medicines Agency (2015-001956-31), the Regional Ethical Committee (H-15007265) and the Danish Data Protection Agency (2012-58-0004).

2.3 | Clinical assessment

Clinical assessment was done by the treating physician and the participant was required to report on sex, age, country of origin to determine ethnicity, height and weight, vascular risk factors (hypertension, type 2 diabetes mellitus, dyslipidemia, alcohol consumption and smoking status), Family history of ischaemic heart disease, previous coronary heart disease, current medication and viral infection history (mode of HCV transmission, HCV GT, viral load, duration of viral infection, previous antiviral treatment). SVR was defined as undetectable levels of HCV RNA 12 weeks after the end of treatment. Clinical characteristics and biochemistry measurements were determined at baseline and 12 weeks after DAA treatment completion.

2.4 | PET/CT assessment of myocardial blood perfusion

The methodology has previously been described (Knudsen et al., 2015). In brief, patients were instructed to abstain from caffeine and methylxanthine-containing substances and medications for at least 12 h before the imaging session.

All PET acquisitions, targeting injection doses of 1100 MBq ^{82}Rb supplied from a CardioGen-82 Sr-82/Rb-82 generator (Bracco Diagnostics Inc.), were obtained in three-dimensional mode on a 128-slice Biograph mCT PET/CT system (Siemens Healthineers) and stored in list-mode format (Murthy et al., 2018). Pharmacologic stressing was obtained using adenosine infused at 140 mcg/kg/min

for 6 min with PET emission acquisition starting 2.5 min into the infusion, Before the rest scans, the patients underwent a low-dose CT for attenuation–correction purposes (120 kVp; effective tube current, 26 mA [11 mAs quality reference]) acquired using a free-breathing protocol (Byrne et al., 2021). Coronary artery calcium score (CACS) images were acquired from a noncontrast breath-hold CT scan and CACS was calculated according to the Agatston score (Agatston et al., 1990). MPR (ml/g/min) was defined as myocardial blood flow (MBF) during stress divided by MBF during rest. The MBF at rest was corrected for baseline cardiac work by dividing the rest MBF by the rate pressure product (RPP), which is the systolic blood pressure times the heart rate, multiplied by 10 000 (Czernin et al., 1993).

All perfusion findings were evaluated by semi-quantitative analysis with Corridor4DM (INVIA), determining the extent and severity of hypoperfusion in addition to the summed scoring system and the total perfusion deficit (TPD). Left ventricular ejection fraction (LVEF) was calculated automatically with Corridor4DM. The MPR was divided into normal (>2.0), borderline (1.5–2.0) or abnormal (<1.5) (Murthy et al., 2011). An ^{82}Rb PET/CT was performed at baseline and between 12 and 24 weeks after DAA treatment completion.

2.5 | Biomarkers related to endothelial dysfunction and cardiovascular risk score

Serum lipids (total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL] and triglyceride) and HCV RNA levels were determined routinely on collected blood and plasma. For the analysis of the following biomarkers; soluble high-sensitivity C-reactive protein (shsCRP), soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble P-selectin (sP-selectin), soluble plasminogen activator inhibitor-1 (sPAI-1) and soluble matrix metallopeptidase 9 (sMMP-9), blood was drawn into EDTA (ethylenediaminetetraacetic acid)-coated Vacuette tubes, separated by centrifuge for 10 min at 3000 rpm within 2 h from the collection and then plasma was stored at −80°C. Analysis for biomarkers was done with two custom-made ProcartaPlex kits (Life Technologies). Framingham risk score (FRS) was calculated as the 10-year risk of coronary disease according to published definitions (D'Agostino RB et al., 2008).

2.6 | Statistics

Categorical variables were reported as absolute numbers and relative frequencies while continuous variables were summarized as median and range (minimum and maximum). Continuous variables were compared using Wilcoxon signed rank test as data were non-normally distributed. All statistics were performed using RStudio (PBC) URL (https://www.rstudio.com/) and p values below 0.05 (two-sided) were considered statistically significant. All data included in this article are available upon request from the authors.

3 | RESULTS

3.1 | Baseline characteristics

A total of 15 patients were included in the study. Ten patients had an Rb PET/CT scan available at baseline and posttreatment and were included in the final analysis. Two patients were excluded since a post-treatment scan could not be performed as it was not possible to obtain intravenous access. In one patient intravenous access and blood samples could not be obtained and therefore the Rb^{82} PET/CT scan was not performed. One patient was included but could not abstain from caffeine before the Rb^{82} PET/CT scan and was excluded. Finally, one patient was included but was lost to follow-up without being scanned. Baseline characteristics of the cohort are shown in Table 1. Nine patients (90%) received DAA treatment for 12 weeks, while one patient (10%) was treated for 8 weeks. All patients achieved SVR after DAA treatment. No cardiovascular events were reported during the study period. Two patients reported previous alcohol consumption above the recommended limit set by the national health authorities.

3.2 | HCV parameters

The HCV characteristics of the included patients are shown in Table 1. All patients achieved SVR after DAA treatment. Two patients (20%) were diagnosed with cirrhosis with no previous record of decompensation. Six patients (60%) had a TE < 7 kPa but were offered DAA treatment due to either severe debilitating fatigue or skin diseases (psoriasis, lichen planus or eczema).

3.3 | Perfusion defects

Perfusion defects were found in three patients (30%). One patient had at baseline a minor reversible defect in the anterior wall of the heart during stress. The TPD was 3% during stress and 0% during rest. Post DAA treatment the defect was still present during stress (TDP = 8%) and reduced but still present at rest (TDP = 4%). The second patient had at baseline a minor apical reversible defect in the heart with hypokinesia (TDP = 9%) during stress that was normalized during rest. The perfusion defect was not detectable after DAA treatment. The last patient had post DAA treatment, a minor reversible defect in the anterior wall of the heart during stress (TDP = 5%) that was not present during rest. The defect was not detectable at baseline. None of the patients had experienced angina pectoris. They were all referred to specialist assessment at the Department of Cardiology where no coronary atherosclerosis requiring further treatment was found.

TABLE 1 Baseline characteristics of the included subjects

	Patients with chronic hepatitis C (n = 10)
Male/female (%)	6/4 (60/40)
Age, years	50 (40–62)
Ethnicity	
Caucasian	8 (80%)
Middle Eastern	2 (20%)
Active smoking	4 (40%)
Previous smoking	4 (40%)
Medication	
Antihypertensive	2 (20%)
Statin	1 (10%)
Antidiabetics	1 (10%)
History of CVD	0
Family history of ischaemic heart disease	4 (40%)
BMI	25.5 (21.0–32.7)
HCV transmission	
IDU	1 (10%)
Sexual	3 (30%)
Tattoo	1 (10%)
Unknown	5 (50%)
HCV genotype	
Genotype 1a	5 (50%)
Genotype 1b	1 (10%)
Genotype 3a	4 (40%)
Liver fibrosis status (Transient Elastography)	
TE < 7 kPa	6 (60%)
TE 7–17 kPa	2 (20%)
TE > 17 kPa	2 (20%)
DAA treatment	
Velpatasvir/sofosbuvir	3 (30%)
Ledipasvir/sofosbuvir/ribavirin	3 (30%)
Ombitasvir/paritaprevir/ritonavir/ dasabuvir/ribavirin	3 (30%)
Sofosbuvir/daclatasvir	1 (10%)

Note: Data presented as number (%) or median and range (min-max).

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DAA, direct-acting antiviral; HCV, hepatitis C virus; IDU, intravenous drug use; TE, transient elastography.

3.4 | Lipid profile, liver parameters and FRS

No significant difference was seen after DAA treatment with respect to total cholesterol, HDL or triglyceride whereas the level of LDL was significant higher after DAA treatment [2.2 mmol/L (1.0–2.5) versus 2.7 mmol/L (1.7–3.9); $p = 0.02$]. A significant decrease in alanine transaminase was seen after DAA treatment [65 U/L (25–126) versus 16 U/L (11–33); $p = 0.002$] whereas no significant difference was seen in relation to levels of albumin and INR. There was a nonstatically significant decrease in the FRS after DAA treatment [10 (2.4–30.0) versus 7.3 (2.8–30.0); $p = 0.23$] (Table 2).

TABLE 2 Lipid profile, liver parameters and Framingham risk score before and after DAA treatment

	Baseline	Post DAA treatment	p
Total cholesterol (mmol/L)	4.2 (2.9–4.7)	4.7 (3.5–6.1)	0.16
HDL (mmol/L)	1.4 (1.0–2.0)	1.3 (0.7–1.6)	0.14
LDL (mmol/L)	2.2 (1.0–2.5)	2.7 (1.7–3.9)	0.02
Triglyceride (mmol/L)	1.7 (1.0–3.5)	1.4 (0.7–2.0)	0.20
Alanine transaminase (U/L)	65 (25–126)	16 (11–33)	0.002
Albumin (g/L)	39 (32–42)	40 (33–44)	0.09
INR	1.0 (0.9–1.2)	1.0 (0.9–1.2)	1
FRS (CVD 10 years, %)	10 (2.4–30.0)	7.3 (2.8–30.0)	0.23

Note: Data presented as median and range (min-max); Wilcoxon signed rank test.

CVD, cardiovascular disease; DAA, direct-acting antiviral; FRS, Framingham risk score; HDL, high-density lipoprotein; INR, international normalized ratio; LDL, low-density lipoprotein.

3.5 | Biomarkers of endothelial dysfunction

The level of s-ICAM1 was significantly lower after DAA treatment [876.3 ng/l (443.6–1862.4) versus 619.4 ng/L (412.7–910.2); $p = 0.004$], whereas no significant changes were seen for shsCRP, sVCAM-1, sMMP-9, sPAI-1 and sP-selectin (Table 3). The analysis of sVCAM-1, sMMP-9, sPAI-1 and sP-selectin were not obtained post DAA treatment in one patient as the plasma sample was lost.

3.6 | ^{82}Rb PET/CT data

Table 3 summarize the findings from the ^{82}Rb PET/CT. The median time from SVR to performed ^{82}Rb PET/CT was 4 weeks (range: 2–12 weeks). All the patients had a MPR within the normal range (>2.0 ml/g/min) at baseline. No difference was seen in either MPR versus [2.9 (2.2–4.1) 3.1 (2.3–4.8); $p = 0.63$] or MPR RPP corrected [2.4 (1.5–4.0) versus 2.1 (1.7–3.0); $p = 0.50$] after DAA treatment. No significant difference was seen in LVEF (rest and stress) or CACS after achieved SVR, but we found that 5 patients (50%) had an ≥5% increase in LVEF between rest and stress after treatment completion compared to 3 patients (30%) at baseline.

TABLE 3 Biomarkers related to endothelial dysfunction and ^{82}Rb PET/CT and quantitative myocardial perfusion data

	Baseline	Post DAA treatment	*p*
shsCRP (ng/L)	172.7 (39.2–1676.8)	263.0 (68.0–2200)	0.13
s-ICAM-1 (ng/L)	876.3 (443.6–1862.4)	619.4 (412.7–910.2)	0.004
sMMP-9 (ng/L)	11.9 (9.5–24.5)	9.2 (5.4– 47.0)	1
sP-selectin (ng/L)	35.1 (18.5–86.9)	23.5 (15.8–60.0)	0.20
sPAI-1 (ng/L)	1.1 (0.8–1.9)	1.3 (0.8–2.5)	0.20
sVCAM-1 (ng/L)	640.2 (347.6–1700.5)	492.7 (362.6–1041.6)	0.30
MPR	3.1 (2.3–4.8)	2.9 (2.2–4.1)	0.63
MPR RPP	2.4 (1.5–4.0)	2.1 (1.7–3.0)	0.50
Difference in LVEF (rest and stress), %	4 (2–9)	5.5 (−2 to 13)	0.34
Systolic blood pressure (mmHg)	132 (107–156)	139 (120–180)	0.24
Agatston (CACS) score	9 (0–141)	6 (0–256)	0.40

Note: Data presented as median and range (min-max); Wilcoxon signed rank test.

Abbreviations: CACS, coronary artery calcium score; DAA, direct-acting antiviral; LVEF, left ventricular ejecting fraction; MPR, myocardial perfusion reserve; RPP, rate pressure product; shsCRP, soluble high sensitivity C-reactive protein; s-ICAM-1, soluble intercellular adhesion molecule-1; sMMP-9, soluble matrix metallopeptidase-9; sPAI-1, soluble plasminogen activator inhibitor-1; sP-selectin, soluble platelet selectin; sVCAM, soluble vascular cell adhesion molecule-1.

4 | DISCUSSION

In this first study of MPR in CHC patients treated with DAA regimens using ^{82}Rb PET/CT we found that levels of MPR did not change after successful DAA treatment indicating that MPR was not severely compromised in this cohort of patients with no previous history of CVD. A recent study (Muñoz-Hernández et al., 2020) including 114 patients with CHC including cirrhotic patients found that markers of endothelial dysfunction decreased after DAA treatment, whereas improvement of subclinical atherosclerosis determined by ankle-brachial index only occurred in patients where atherosclerosis was present at baseline. In our study, none of the patients had a primary history of CVD. In the two patients with perfusion defects at baseline, suggestive of obstructive cardiovascular disease, improvement of the MPR was only seen in one patient whereas MPR decreased in the other patient after DAA treatment. Overall, no significant improvement was seen in relation to decreased levels of shsCRP, sMMP-9, sPAI-1, sVCAM-1 and sP-selectin after DAA treatment. We found a significant decrease in levels of sICAM-1 after DAA treatment which has also been seen in a previous study including patients coinfected with HIV who received treatment with pegylated-interferon and RBV (Chew et al., 2014). The decrease in levels of sICAM-1 could be due to the cessation of liver inflammation and pro-inflammatory effect caused by viremia which occurs after viral eradication. However, due to the small patient cohort, the importance of this finding is uncertain and must be verified in a larger patient cohort.

Our cohort did not have known CVD at the time of inclusion although 8 (80%) patients had well-known risk factors for the development of CVD like diabetes, hypertension, hypercholesterolemia or previous or current smoking. Our results may indicate that MPR is not compromised in patients with CHC and no previous CVD and a low FRS (<10%). It would, however, be interesting to further evaluate the influence of CHC on CVD in a larger cohort including patients with liver cirrhosis and a healthy control group matched according to known risk factors to CVD. In patients with rheumatoid arthritis and lupus erythematosus, who may share inflammatory risk factors with CHC patients were a significant lower MPR compared to healthy controls found and this reduction correlated with disease duration (van Leuven et al., 2008). The included patients in the study had all been diagnosed with CHC > 5 years but it might be the case that longer disease duration is needed for coronary atherosclerosis development and that patients with disease duration extending over decades should be included to detect notable differences in MPR after DAA treatment.

Interestingly, we found a tendency to a change in lipids levels to a more atherogenic profile with an increase in total cholesterol and LDL. Hepatitis C virus alters the cellular lipid metabolism to gain a more lipid-rich intracellular environment which is necessary to facilitate the virus' own multiplication (Syed et al., 2010). This can create a “false” protective atherogenic profile that is restored by eradicating the HCV (Campo & Romero-Gómez, 2015; Muñoz-Hernández et al., 2020; Syed et al., 2010). As expected, levels of alanine transaminase decreased after DAA treatment whereas no significant changes were seen in relation to albumin and INR. The majority of included patients had mild or moderate liver fibrosis which could explain why the synthetic function of the liver was not severely affected before the initiation of DAA treatment (Tacke et al., 2020).

A limitation in this study is the short follow-up period where ^{82}Rb PET/CT was conducted between 2 and 12 weeks after SVR and the size of the cohort. It is possible that a longer follow-up period would reveal changes in MPR that are not detectable shortly after viral eradication. The study design was not set up to determine the impact that SVR has on the prevention of cardiovascular events. This would require a longer follow-up period with a larger patient cohort.

In our study, successful DAA treatment did not improve MPR in patients with CHC with no previous history of CVD and normal pretreatment MPR in the given time frame where the patients were followed. We found a tendency to decreased levels of biomarkers of endothelial dysfunction and inflammation and increased levels of total cholesterol and LDL after DAA treatment, but future studies including larger patient cohorts with longer follow-up are warranted to elucidate the effect of SVR on coronary microvascular function and biomarkers on endothelial dysfunction.

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CONFLICT OF INTEREST

Nina Weis has been clinical investigator, lecturer or on advisory boards for Abbvie, Gilead, Glaxo Smith Kline and Merck Sharp Dohme and has received unrestricted grants for research from Abbvie and Gilead without relation to the present work. Anne-Mette Lebech has been a member of advisory boards for and has received speakers' honorary fees from Pfizer, GSK, MSD and Gilead without relation to the present work and for the remaining authors there are no conflict of interests. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

DATA AVAILABILITY STATEMENT

The data presented in this study are available on request from the corresponding author.

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