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Short Communication

Status of Central and Peripheral Hemodynamics Among Elderly Patients with Heart Failure and Stable Left Ventricular Systolic Function Treated with 3D - Antiviral Therapy of Chronic Viral Hepatitis C (HCV)

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Abstract

Results of HCV antiviral therapy with Direct Antiviral Agents (DAAs) (Viekira Pak) among elderly patients with heart failure are observed in the article. The evaluated group of patients was traditionally out of therapy scope in interferon + ribavirin era. We assessed safety, compliance and efficacy of HCV Genotype 1 antiviral therapy with Viekira Pak in the targeted population group as well as the status of central and peripheral hemodynamics during the course of therapy and follow-up period.

Introduction

Current HCV antiviral therapy with DAAs significantly expanded treatment potential considering opportunities to reach SVR in multiple patients' subgroups [1,2]. Chance to be cured was given to HCV patients who were considered to become candidates on treatment as former therapy basis - alpha-interferons were either contraindicated or associated with extremely high risk of complications. Thus, patients with autoimmune and chronic inflammatory intestines diseases, severe arterial hypertension and endocrine system pathologies had no treatment opportunities.

Our major attention was paid to special subgroup of elderly patients over 60 years with such common co-morbidities as arterial hypertension, coronary insufficiency of different degrees, heart failure and diabetes mellitus 2nd type, etc. No research of HCV antiviral treatment with DAAs among patients with cardiovascular pathologies was held. Although in some multicenter protocols (usually phase III clinical studies) patients over 60 years were separated from general randomized pool and assessed on standard parameters: SVR, Severe Adverse Events (SAE), discontinuation rate caused by SAE, etc. At the same time data from those studies did not reflect comorbidities, especially detailed analysis of central and peripheral hemodynamics.

Question about HCV therapy for patients with chronic heart failure is considered to be crucial. Obviously, decision to start treatment has to be made individually based on level of circulatory insufficiency, calculated life expectancy, direct contraindications, kidney functions and proposed Drug-Drug Interactions (DDIs). The Aim of current investigation was to assess the influence of direct antiviral HCV therapy with 3D/Viekira Pak (Dasabuvir 250 mg + Ombitasvir 12,5mg + Paritaprevir 75 mg / Ritonavir 50 mg) on parameters of central and peripheral hemodynamics among patients with heart failure and stable left ventricular systolic function. We separated this group of patients from general pool who received DDAs for HCV Gt 1a/b treatment in real world practice.

Keywords: Chronic Heart Failure, Sustained Virologic Response (SVR), Chronic Viral Hepatitis C Genotype 1 (HCV Gt 1)

Materials and Methods

32 patients (28 males and 4 females, aged 64.3+1.2 years) were enrolled with II functional class of chronic heart failure, left ventricular ejection fraction > 45%, II-III functional class of effort angina and sinus rhythm, clinically and laboratory symptoms of HCV Gt1a/b. Before start of Viekira Pak therapy (strictly according to USPI 19/12/2014) the following laboratory examination was made: clinical blood test and metabolic panel, anti-HCV_{total} (ELISA, «Roche»), HCV RNA, IU/ml and HCV genotype (Cobas Amplicor, «Roche»), transient liver elastometry to explore METAVIR fibrosis score («Fibroscan M10», France; F-grade). Atenolol 50 mg daily as a part of "cardiac" therapy extended to 80-100 mg daily to reach target heartbeat ≤ 60 per minute was one more significant parameter of targeted patients group.

Applanation tonometry («SphigmoCor», USA) was used to measure arterial stiffness and central blood pressure. Carotid-femoral pulse wave velocity (PWV_{cf}) (m/sec) was also evaluated. Following parameters were calculated automatically: subendocardial viability ratio (SEVR, %), systolic and diastolic pressure time index (PTI-sist, PTI-diast; mm. Hg x sec.), ejection duration (ED, ms), central systolic and diastolic arterial pressure (cSAP, cDAP;, mm. Hg), central pulse pressure (cPP, mm. Hg), central augmentation index standardized to heartbeat rate 75 per minute (cAI - 75/min), pulse pressure index (PPI ampl., %) and time to arterial wave reflection (tR, msec). Tredmill test Bruce protocol was executed complementary. Two-dimensional echocardiography (EDS LV, ESS LV mm) (Hitachi - M12, Japan) was used to evaluate left ventricular ejection fraction (EF LV, %) and heart cavity sizes - end-systolic and end-diastolic volumes.

SPSS Statistics 19.0 was used for statistical processing of received data during our research. Quantitative derivates were described by means of median line (Med) and 25 and 75 percentiles (interquartile interval - CI). We used Mann-Whitney and Wilcoxon non-parametric critical values to assess statistical significance. Diversity was recognized valid with $p<0.05$ level of significance. Period of observation was 24 weeks: 12 weeks of therapy with 3D and 12 weeks follow-up to assess SVR and key indices of central and peripheral hemodynamics. Baseline demographic and clinical patients' parameters are presented in Table 1.

Parameter	Number of patients
Age, years (Med)	64.3+1.2 years
Male, n Female, n	28 14
Weight, kg (Med)	84.3+2.6
Effort angina II-III function class, n (%)	32 (100%)
Arterial hypertension, n (%)	32 (100%)
Dyslipidemia, n (%)	27 (84%)
Heart attack in anamnesis, n (%)	18 (56%)
Chronic obstruction liver disease, n (%)	4 (12%)
Diabetes mellitus, type 2, n (%)	9 (28%)
Components of chronic heart failure therapy, n (%) - antiaggregants - diuretics - statins - APF inhibitors - atenolol	 32 (100%) 25 (78%) 20 (62%) 30 (93%) 32 (100%)
HCV RNA, IU/ml <800.000, n (%) >800.000, n (%)	 11 (34%) 21 (66%)
HCV Genotype 1a, n (%) 1b, n (%)	 3 (9%) 29 (31%)
METAVIR fibrosis stage F0 n (%) F1 n (%) F2 n (%) F3 n (%) F4 n (%)	 0 2 (6%) 10 (31%) 6 (18%) 14 (45%)
Platelet count < 90.000, n (%) > 90.000, n (%)	 8 (25%) 24 (75%)
ALT, IU/ml	84.3 + 9.8

Table 1: Baseline demographic and clinical parameters of patients with HCV Gt1a/b and concomitant chronic heart insufficiency.

All the patients (Table 1) were aged over 60 and suffered from chronic heart failure. All of them suffered from arterial hypertension and effort angina. Majority (27 patients - 84%) had laboratory abnormalities typical for hyperlipidemia Fredrickson classification type IIb and more than a half (18 patients - 56%) had heart attack in anamnesis. Clinical manifestations of diabetes mellitus type 2 were observed among 9 patients (28%) and almost all of them were obese. Overall, our patients' pool could be referred to difficult-to-treat population due to all confirmed comorbidities - dyslipidemia, arterial hypertension, diabetes mellitus type 2 and obesity - independent and significant predictors for HCV progression to cirrhosis and hepatocellular carcinoma [3,4]. Age of patients turned up to be complementary independent factor for HCV progression. It is known that progression exponential curve increases by 0,35 - 0,5 points every 5 years from start of fibrosis assessment in absence of other factors accelerating fibrosis. We observed minimum 3 independent and significant predictors of fibrosis progression in our group in conditions of natural HCV development. Transient elastometry with METAVIR score confirmed it as 14 patients (45%) had compensated liver cirrhosis (Child-Pugh A) and 6 patients (18%) were on fibrosis 3 (F3) stage. Thus, 20 patients (63%) demonstrated advanced stage of liver disease.

All 14 cirrhotic patients were infected with HCV Gt 1b, each of 3 patients with Gt1a had F2. This data became the basis for choice of treatment regimen. All Gt1b cirrhotic patients received Viekira Pak + ribavirin for 12 weeks. 3 patients with Gt1a did not have cirrhosis and followed the same regimen. The other 15 patients with Gt1b and no cirrhosis used Viekira Pak for the same 12 weeks but without ribavirin. All patients from our group reached SVR12. All patients tolerated treatment rather well: no adverse events which caused discontinuation or dose modification of HCV regimen were registered. Rarely indicated (2 out of 32 patients) minor nausea and headache could not be correlated with antiviral therapy. Evaluation of central and peripheral hemodynamics during the course of Viekira Pak therapy and 12 weeks after end of treatment was a complementary but not secondary goal of our research. Assessed parameters of central and peripheral hemodynamics are demonstrated in Table 2.

Parameter	Before Start of 3D Therapy	12 Weeks After End of Treatment	P
PWV_{cf}, m/sec	15.1 (13.0;16.4)	14.1 (12.3;15.9)	0.003
SEVR, %	150.0 (134;179)	146.0 (129;170)	0.703
PTI_{sist}, mm.Hg x sec	2354.0 (2031;2683)	2743.0 (2405;2979)	0.001
$PTI_{diast.,}$ mm.Hg x sec	3682.0 (3263;3827)	4079.0 (3973;4113)	0.001
cPP mm.Hg	51.0 (40;59)	45.0 (33;55)	0.208
cAI - 75/min, %	32.0 (26;35)	22.0 (21;28)	0.002
PPI amplif., %	129.0 (121;138)	114.0 (112;122)	0.002
ED, ms	279.0 (264;287)	322.0 (307;326)	0.001
cSAP, mm.Hg	130.0 (125;139)	115.0 (112;118)	0.004
cDAP, mm.Hg	82.0 (77;82)	70.0 (64;78)	0.058
tR, msec	144.0 (127;159)	145.0 (128;154)	0.406
EF LV, %	49.0 (48.5;52.0)	53.0 (48.5;55.0)	0.001
EDS LV, mm	41.0 (37.5;45.0)	40.0 (37.0;45.0)	0.173
ESS LV, mm	35.0 (27.5;35.5)	31.0 (26.5;32.5)	0.001
H.b.f/min	78 (72;82)	52 (50;55)	0.001

Note: PWV_{cf}, m/sec - carotid-femoral pulse wave velocity; SEVR - subendocardial viability ratio; PTI_{sist}, mm.Hg x sec - systolic pressure time index; PTI_{diast}., mm.Hg x sec - diastolic pressure time index; cPP, mm.Hg - central pulse pressure; cAI- 75/min.,% - central augmentation index; $PPI_{amplif.,}$ % - pulse pressure index; ED, ms - ejection duration; cSAP, mm.Hg - central systolic arterial pressure; cDAP, mm.Hg - central diastolic arterial pressure; tR, msec - time to arterial wave reflection; EF LV, % - left ventricular ejection fraction, EDS LV, mm - left ventricular end-diastolic volume, ESS LV, mm - left ventricular end-systolic volume; H.b.f/min - heart beat rate

Table 2: Parameters of central and peripheral hemodynamics during the course of HCV 3D treatment and concomitant therapy of chronic heart failure and 12 weeks after end of treatment.

The following conclusions could be made after analysis of the data, presented in Table 2. We did not modify heart failure and hypertension therapy (primarily, no discontinuation of previously prescribed drugs was made) during the full course of antiviral therapy. Objected heartbeat rate and valid decrease of systolic and diastolic arterial pressure was reached in 24 weeks after start of treatment (12 weeks after end of treatment). Increase of ejection fraction and decrease of left ventricular end-systolic volume are also worth mentioning. All patients from our pool had stable effort angina, so the objected heartbeat rate was 55-60 strokes per minute. Beta-blockers and other pulse slowing drugs are associated with valid decrease of mortality in large randomized multicenter clinical studies among patients with chronic heart failure [5]. But despite of current clinical recommendations, usage of beta-blockers in real world is insufficient, which turns to inadequate control of heartbeat rate.

Enrolled patients had concomitant HCV (mostly on advanced stages) and chronic heart failure. Both diseases require drug therapy. The main question - how would antiviral treatment influence on heart failure therapy? And the other way round - what would be the impact of heart failure therapy for patients with stable ejection fraction on results of HCV treatment - reaching SVR?

Received data confirmed no impact of heart failure therapy on results of HCV treatment - all patients have reached SVR! Moreover, heart failure therapy at chosen endpoint (12 weeks after end of HCV treatment) was effective and safe. Parameters of central and peripheral hemodynamics were evidently improved. Potential influence of HCV therapy on hemodynamics in targeted patients' group is the question of special interest. Thus, average duration of chronic heart failure therapy before start of HCV treatment was 28.4+3.7 months. We chose HCV therapy as primary endpoint for analysis of central and peripheral hemodynamics parameters. We received the following results: achievement of objective heartbeat rate, decrease of systolic and diastolic arterial pressure, augmentation of left ventricular ejection confirmed by valid increase of Ejection Duration (ED) and increase of Left Ventricular Ejection Fraction (LVEF). Is it suitable to conclude that HCV therapy itself positively influences on chronic heart failure therapy in chosen patients' pool?

Possibility of myocardium damage among HCV infected patients was mentioned as one of extra hepatic manifestations of hepatitis C [6]. Different variants of HCV-associated cardiomyopathy were described: from clinically significant, rarely fatal forms to subclinical, diagnosed only by means of special instrumental tests [7,8,9]. Immense improvement of hemodynamics among patients with HCV-associated cardiomyopathy against the background antiviral therapy with interferon-alpha + ribavirin and basic treatment of heart failure is an additional argument for above mentioned statement [10,11]. However, the number of such observations is low because usage of interferon-alpha and ribavirin was interfacing with severe adverse events.

In our opinion, submitted data could indirectly indicate potential impact of HCV infection on heart failure progression as far as successful HCV eradication in our research was associated with valid improvement of hemodynamics parameters exactly during the course of HCV therapy and follow-up period whereas in contrast in antecedent period of heart failure therapy (almost twice longer than the period of our trial) had not demonstrated such positive changes. Nevertheless, we understand that confirmation of our proposal requires additional trials with other design - comparison of heart failure treatment efficacy among patients with HCV, who receive and do not receive direct antiviral agents.

From the other hand results of the research move us to obvious conclusions:

1. HCV antiviral therapy with Viekira Pak among patients over 60 years with concomitant chronic heart failure and stable ejection fraction is safe and effective.
2. HCV antiviral therapy with Viekira Pak does not require modifying therapy of chronic heart failure for patients over 60 years with stable ejection fraction.

Our data enable to expand the pool of patients with HCV Gt 1 for antiviral treatment with direct antiviral agents.

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