Sapporo Medical Journal
Volume 55, Issue 07, July 2021

Effects of Direct Antiviral Agents on Hepatitis C virus arthropathy

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Abstract— The aim of this study was to assess the potential efficacy of new drug therapy of HCV in treatment of HCV arthropathy and to find out if sero-conversion is related to relief of patients symptoms.Patients having chronic hepatitis C infection with arthropathy underwent thorough medical history and clinical examination. The following tests performed; C - reactive protein, erythrocyte sedimentation rate, liver function tests, HCV antibody test, polymerase chain reaction for HCV and rheumatoid factor. The included patients received the treatment of HCV in the form of dual therapy (Sofobuvir, Daclatasvir) or triple therapy (Sofobuvir, Daclatasvir and Ribavirin) for 3 months as secheduled. The patients underwent repeated clinical examination and laboratory assessment after completion of the treatment course and the achievement of sustained virological response (SVR).The most frequent affected joints were the proximal inter-phalangeal (PIP) and the matacarpo-phalangeal (MCP) joint.On assessment of the patients' laboratory data before antiviral therapy and after SVR, there were statistically high significant improvement in the liver function tests, ESR and the number of RF positive cases. The joint affection frequencies showed also statistically high significant improvement.The current study concludes the high efficacy of the new drug therapy of HCV in treatment of HCV arthropathy, with significant reduction in joints affection and improvement of the inflammatory markers and the immunological profiles.

KEYWORDS: HCV, arthropathy, new treatment.

1. INTRODUCTION

The released Egyptian Demographic Health survey (EDHS) reported HCV infection prevalence of 14.7% in Egypt [1]. HCV was documented to have both lymphotropic and hepatotropic effect. It was supposed that HCV virus may act as a stimulus triggering the immune system chronicly [2].

Variable rheumatic manifestations can be induced by chronic HCV infection. Several hypotheses were proposed for this process. First, HCV joints infection leading to HCV arthritis. Second, these manifestations is specifically attributed the the chronic inflammation state triggered by HCV infection. Third, the HCV infection and arthritis may chancly co-exist. Finally, HCVmay be the trigger for reumatic disease devolopment in persons who are genetically predisposed [3]. Thus, investigations for HCV should be carried out in patients with rheumatic manifestations [4].

The new direct acting drugs (DADs) have been considered presently to treat HCV genotype 4 in Egypt, and they have shown excellent results regarding the HCV seroconversion. These wereeither sofosbuvir and daclatasvir only (Dual therapy), or combined with Ribavirin(triple therapy)[5].

The current study was undertaken to find the potential efficacy of new drug therapy of HCV in the treatment of HCV arthropathy and to find out if sero-conversion is related to relief of patients symptoms.

2. MATERIALS AND METHODS

2.1 Study design:

This is an observational descriptive longitudinal study that was conducted after the achievement of regional ethical committeeapproval and it was performedaccording to the Declaration of Helsinki. Patients having chronic hepatitis C infection with arthropathy those attended the Rheumatology unit, Internal Medicine department, EL Raghy hospital in Assiut University Hospitals in the period from January 2018 to January 2020 were eligible for the study. Patients were considered as having HCV infection if they were positive for HCV antibodies and polymerase chain reaction for HCV (PCR HCV).

Patients who were previously established as having rheumatoid arthritis (RA) as beingfulfilling the criteria of the Americancollege 2010,and those who were positive for anti-cyclic citrullinated peptide (anti-CCP) were excluded from the study. Also patients aged above 65 years, patients with significant functional compromise (child-pugh B and C), patients with organ failure, patients with chronic infection such as tuberculosis, patients with concomitant hepatitis B virus and patients on immunosuppressive drugs were excluded from the study.Finally one hundred patients were included in this study.

A written informed consent was obtained from each patient and confidentiality was assured for all patients.

The included patients underwent dedicated medical history analysis and thorough clinical examination. Specifically, the rheumatologic manifestation was analyzed; site of affection, onset, course and duration, and the occurrence of morning stiffness for more than one hour.

Venous samples were withdrawnfrom each patient to have the following tests performed; CRP, ESR, liver function tests, HCV antibodyandPCR HCV tests. Rheumatoid factor (RF) was also investigated.

2.2 Rheumatoid factor (RF) assessment

RF was assayed in the patients' sera those were previously stored at - 80°C, with a quantitative immune-nephelometry. If the concentration exceeded the cut-off value provided by the used kit (8 IU/ml), the test was considered to be RF.

The included patients received the treatment of HCV in the form of dual therapy (Sofobuvir, Daclatasvir) or triple therapy (Sofobuvir, Daclatasvir and Ribavirin) for 3 months as scheduled from the ministry of health. The patients underwent repeated clinical examination and laboratory assessment after the achievement of sustained virological response (SVR).

2.3 Study outcomes

The primary outcome of this study was the effect of the cure of HCV denoted by SVR on the rheumatologic manifestations of the study patients. The secondary outcome was the change in the laboratory and immunological profile of the patients after SVR.

2.4 Statistical analysis

Data of the patients were collected, and suitable statistical analysis was done using the SPSS software (version 22).Mean,standard deviation (for numerical data) and percentages (for categorical data) were calculated. Paired t-test and Chi-square test were used as appropriate to compare between the various parameters before treatment and after SVR. A significance level of 0.05 was considered in the results interpretation.

3. RESULTS

The mean age of included patients was 41.26 ± 9.5 years. Patients' demographic and basal clinical data were illustrated in table 1.

Table (1): Demographic and clinical data of the studied subjects and the received treatment

	All patients (n=100)
Age (years)	
Range	21 - 75
Mean ± SD	41.26 ± 9.5
Gender	
Male	42 (42 %)
Female	58 (58 %)
Comorbidities	
Diabetes mellitus	14 (14%)
Hypertension	27 (27%)
Ischemic heart disease	3 (3%)
Clinical datarelated to HCV	
Jaundice	26 (26%)
Pallor	30 (30%)
xerophthalmia	5 (5%)
Xerostomia	5 (5%)
Fever	5 (5%)
Hepatomegaly	65 (65%)
Splenomegaly	5 (5%)
Clinical datarelated to HCVarthropathy	
Arthritis	22 (22%)
Arthralgia	78 (78%)
Morning stiffness > 1/2 hr.	9 (9%)
Purpuric eruptions	5 (5%)
Myalgia	8 (8%)
Received treament	
Dual therapy	54 (54%)
Triple therapy	46(46%)

The most frequent affected joints werethe proximal inter-phalangeal (PIP) and the matacarpo-phalangeal (MCP) joint, each of them was affected in 90 cases (90%). Frequencies of joints affection in the studied cases were demonstrated in table 2.

Table (2): Frequency of Joint Affection in studied cases:

Joint	Number (%)	Arthralgia	Arthritis
Upper limb			
PIP	90 (90%)	81 (81%)	9 (9%)
MCP	90 (90%)	83 (83%)	7 (7%)
Wrists	60 (60%)	57 (57%)	3 (3%)
Elbows	23 (23%)	21 (21%)	2 (2%)
Shoulders	25 (25%)	23 (23%)	2 (2%)
Lower limb			
MTP	4 (4%)	4 (4%)	0 (0%)
Ankle	10 (10%)	8 (8%)	2 (2%)
Knee	57 (57%)	41 (41%)	16 (16%)

Hip	17 (17%)	17 (17%)	0 (0%)

The joint affection frequencies before treatment and after SVR were compared. Statistically high significant reduction in affection frequencies were demonstrated in most of the affected joints (*P* value < 0.01), this was more evident at the upper limb (table 3).

Table (3): Frequency of joint affection andrheumatologic manifestations in studied cases before treatment and after SVR

Joint	Before treatment N (%)	After SVR N (%)	p
Affected joints			
PIP	90 (90%)	24 (24%)	<0.001
MCP	90 (90%)	19 (19%)	<0.001
Wrists	60 (60%)	23 (23%)	<0.001
Elbows	23 (23%)	7 (7%)	<0.001
Shoulders	25 (25%)	5 (5%)	<0.001
MTP	4 (4%)	0 (0%)	0.12
Ankle	10 (10%)	4 (4%)	0.031
Knee	57 (57%)	36 (36%)	<0.001
Hip	17 (17%)	10 (10%)	0.016
Rheumatologic manifestations			
Arthritis	22 (22%)	10 (10%)	0.021
Arthralgia	78 (78%)	34 (34%)	<0.001
Morning stiffness > 1/2 hr.	9 (9%)	3 (3%)	0.07
Purpuric eruptions	5 (5%)	3 (3%)	0.74
Myalgia	8 (8%)	2 (2%)	0.051

PIP; proximal inter-phalangeal, MCP; metacarpo-phalangeal, MTP; metatarso-phalangeal.*P* value considered of statistically non-significant if >0.05, significant if < 0.05 and highly significant if < 0.01.

On assessment of the patients' laboratory data before treatment and after achievement of SVR, there were statistically high significant differences in the bilirubin, hepatic enzymes levels and the viral load as well as theESR and the number of CRP and RF positive cases (*P* value < 0.01) (table 4).

Table (4): laboratory parameters in studied cases before treatment and after SVR

Test	Before treatment	After SVR	p
Liver function tests& PCR			
Bilirubin (mg%)	1.7± 0.05	1.3± 0.04	<0.001
AST (U/L)	46.62± 21.28	32.05± 25.24	<0.001
ALT (U/L)	46.49± 30.41	29.43± 23.75	<0.001
PCR	$5.3*10^6$± 9.3 $*10^6$	12.76± 4.209	<0.001
ESR (ml/h)			
First hour	55.54± 16.84	35.80± 9.49	<0.001
Second hour	57.56±17.23	34.80± 7.99	<0.001
CRP positive	98 (98%)	47 (47%)	<0.001
RFpositive	69 (69%)	56 (56%)	0.004

AST; aspartate transaminase, ALT; alanine transaminase, PCR; polymerase chain reaction.*P* value considered of statistically non-significant if >0.05, significant if < 0.05 and highly significant if < 0.01.

4. DISCUSSION

Rheumatologic manifestations association with HCV infection is not that common. The pathogenesis of such process is still puzzling. Additionally, similarity of rheumatologic symptoms and signs of HCV arthropathy to RA manifestations was addressed. However, anti-CCP is assumed to be highly specific for RA diagnosis.

This study included 100 patients having HCV arthropathy. The mean age of study group was 41.26 ± 9.5 years, with female predominance; 58%. This is in line with a previous report that considered female sex as a risk factor for the HCV infection extrahepatic manifestations occurrence [6].

In the current study, arthralgia was the most commonpatients symptoms, being experienced by more than three quarters of the study patients. The small joints of the hand; PIP and MCP joints were the most frequently affected joint (90% of patients for each). This is in accordance to the documented resemblance of joint affection pattern in both HCV arthropathy and RA [4].

The present study revealed that, after SVR achievement, there was statistically high significant reduction in affection frequencies in most of the affected joints as well as significant/high significant improvement of most of the arthropathy manifestations.

There is scarce evidence about the effects of DADs on HCVarthropathy. A recent Egyptian study concluded that the use of new antiviral DADs (either the dual or the triple therapy) is an effective treatment regimen, successfully eradicated the HCV infection and improved the HCV arthropathy manifestations [7]. Another recent Egyptian study was conducted to assess the extra-hepatic manifestations in patients with HCV and treated either by sofosbuvirbased treatment regimen or by the traditional interferonbased regimen. They reported the significant improvement in the articular in sofosbuvir based treatment regimen group after completion of the treatment [8].

In consistency with the current study, a retrospective American study involved patients having HCV arthropathy. They found that there was significant improvement in the joint related symptoms and reduction in prescriptions of opioids after treatment with DADs [9].

Concerning the laboratory analysis in the present study, statistically significant differences in the liver function tests and the viral load as well as the ESR and the number of CRP positive cases were noted.

The study of Ahmed et al. (2018) showed similar findings. They reported significant reduction in hepatic enzymes levels after DADs completion [5]. Also, the study of Mehta et al. (2017) emphasized on the efficacy of DADs in treatment of chronic hepatitis C infection with transaminases significant improvement [10].Previous studies revealed that both inflammatory parameters could show improvement after the eradication of HCV infection [11–13].

Serum RF in the present study was positive in 69% of patients. Statistically high significant reduction was noticed in the frequency of patients positive for RF after SVR to reach 56%. According to several previous studies, HCV arthropathy was associated with high frequency of RF positive cases [14-16]. In regard to the significant reduction of the RF positive patients after SVR, this was in consistency with a previous study investigated patients with extrahepatic manifestations of HCV, the authors reported normalization of RF levels in 50% of patients after completion of DAAs treatment [17]. Similar results were also documented by Fathi et al. (2020), they showed that RF levels showed a reduction from 42.2% to 18.6%,after treatment of patients with HCV by the DADs [18].

5. CONCLUSION

The current study concludes the high efficacy of new drug therapy of HCV in treatment of HCV arthropathy, with significant reduction in joints affection frequency and improvement of the patients symptomatology, the inflammatory markers and the immunological profile.

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