Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2023.182913.2706 Volume 29, Issue 5, September 2023
Manuscript ID ZUMJ-2212-2706
DOI **10.21608/ZUMJ.2023.182913.2706**

ORGINAL ARTICLE

Impact of HCV Eradication on Rheumatoid Arthritis Activity in Rheumatoid Arthritis Patients with Concomitant HCV Infection

Dena Mahmoud Abd El Ghafar[1],Islam Abd El- Hamid Salah El-Zayyadi[2] ,Aya Ahmed Fathy[3],Sherine Mohamed Gaafar[1],Eman Bakr Elmarghany[1]

[1] Department of Rheumatology, Rehabilitation and Physical medicine, Faculty of medicine Mansoura University, Egypt.

[2] Department of Internal medicine, Gastroenterology and Hepatology unit, Faculty of medicine, Mansoura University, Egypt.

[3] Department of Public health and Preventive medicine, Faculty of medicine, Mansoura University, Egypt.

Corresponding author:
Reprints and proofs are to be sent to Reprints and proofs are to be sent to Dena Mahmoud Abd El Ghafar, MD, Lecturer of Rheumatology, Rehabilitation and Physical medicine, Mansoura University, Egypt.
Tel: 01000136696
E.mail:
dr.denamahmoud@gmail.com

Submit Date 2022-12-24
Revise Date 2023-02-17
Accept Date 2023-02-25

ABSTRACT

Background and aim of work: Rheumatoid arthritis (RA) patients with concomitant hepatitis C virus (HCV) infection tend to have higher disease activity than patients with no HCV. This study aimed to explore the potential outcome of elimination of HCV on RA disease activity in the patients with comorbidity of RA and HCV infection.

Methods: This is a retrospective study. The medical records of 55 RA patients with concomitant HCV infection were reviewed. RA clinical and laboratory parameters of RA activity and disease activity score-28 (DAS28) were obtained from the medical records before the initiation of the anti-viral treatment and 12-weeks after completing antiviral therapy for HCV.

Results: After treatment, the sustained virological response 12-weeks (SVR12) was achieved in 83.6% of the patients. Good and moderate response based on EULAR response criteria was achieved in 76% of the RA patients. In RA patients achieved SVR12, there was a significant post-treatment decline in the RA activity measures including morning stiffness duration ($p < 0.001$), presence of subcutaneous nodules ($p < 0.001$), C - reactive protein (CRP) level ($p<0.001$) and erythrocyte sedimentation rate (ESR) level ($p < 0.001$) as compared to pre-treatment values. The DAS28-ESR was significantly decreased from 4.15 ±1.31 at the pretreatment to 3.08 ±1.28 after achieving SVR12 ($P=0.004$). The pretreatment viral load and attainment of SVR12 were the only factors that could predict improvement of RA activity in regression analysis.

Conclusion: Elimination of HCV is associated with significant improvement in RA activity in chronic HCV infection patients with concomitant RA.

Keywords: Hepatitis C virus infection; rheumatoid arthritis; disease activity score.

INTRODUCTION

Hepatitis C virus (HCV) infection represents one of the major health problems in Egypt, where it displays one of the highest prevalence rates globally [1]. In 2008, surveys demonstrated that anti-HCV sero-prevalence in the Egyptian population was around 14.8%, indicating their exposure to the HCV, and approximately 9.7% in the age group of 15 to 59 years had chronic HCV infection [2]. Attempted to find solutions to this major health, social and economic challenge, Egypt initiated a national control program for elimination of HCV in 2008. In 2014, Egypt launched another ambitious national strategy focused on aggressive screening and treatment program for HCV eradication as a public health threat by 2021. In 2015, the Egyptian Health Issues Survey re-estimated the prevalence of HCV infection and revealed that approximately 7% of the Egyptians in the age between 19 and 65, nearly four million people, had chronic HCV infection [3].

Rheumatoid arthritis (RA) may co-exist with HCV infection by chance, as both conditions are relatively common diseases, or may be attributed to

the potential ability of HCV to initiate RA in the individuals with genetic susceptibility [4]. The co-morbidity of RA and HCV infection can lead to significant impact on the clinical outcomes of RA. In one hand, patients with HCV commonly develop arthralgia, arthritis, or vasculitis [5], and hence, HCV infection augmented the clinical manifestations of RA. Furthermore, RA patients with concomitant HCV had increased rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA) titers due to chronic clonal B-lymphocyte expansion [6]. Therefore, patients with comorbidity of RA and HCV infection likely to have more disabling symptoms and higher activity scores mainly due to higher pain levels, tender joint counts, and patient global assessment [7].

On the other hand, treatment to target strategy for management of RA requires the use of immunosuppressive agents that could potentially raise the risk of hepatotoxicity [8], and viral flare [9]. Therefore, it can be assumed that RA patients with comorbid HCV infection may demonstrate higher activity and severity measures as a result of altered treatment pattern in these patients.

Gathering these data together, we hypothesized that elimination of HCV infection may improve disease activity in patients with comorbidity of RA and HCV infection. However, the data regarding effect of elimination of HCV infection on RA activity are scanty. Additionally, there is not any conclusive evidence concerning how treating HCV will affect RA activity. Egypt, where HCV infection is common, makes for an excellent place for research on this relation.

This work aimed to assess the potential effect of elimination of HCV on RA disease activity in patients with comorbidity of RA and HCV infection.

MATERIALS AND METHODS

Study Population

This is a retrospective study that comprised 55 RA patients with HCV co-infection attended to the Rheumatology and Rehabilitation Outpatient Clinics, Mansoura University Hospitals, Egypt. The medical records of these patients were reviewed in the period from May 2021 to May 2022. The diagnosis of RA was made according to 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria [10]. Virological diagnosis of chronic HCV infection was based on two laboratory tests: the serological assay of HCV antibodies and the real-time polymerase chain reaction (PCR) assay for HCV-RNA detection [11]. The regional ethical committee of Mansoura University gave its approval to the study's methods and design (Acceptance code: R.22.10.1889 - 2022/10/07).When conducting this study, all investigators adhere to the Declaration of Helsinki's ethical guidelines.

Patients with cirrhosis, hepatocellular carcinoma, undetermined focal hepatic lesion, hepatitis B virus coinfection, human immunodeficiency virus coinfection, impaired renal function, malignancy, bleeding diathesis, hemoglobinopathies or patients on hemodialysis were excluded from the study. None of the patients enrolled in this study were using methotrexate, or leflunomide during the study period.

Data Collection

Data collection included personal data, duration of RA, morning stiffness duration and current RA medications. The VAS-pain score and the swollen/tender joints counts were recorded. The RA activity score 28 based on erythrocyte sedimentation rate (ESR) level (DAS28-ESR) was recorded for all patients. If DAS28-ESR is <2.6, the patient was considered to be in remission. A DAS28-ESR $\geq$ 2.6 to $\leq$ 3.2 indicates low disease activity, > 3.2 to $\leq$5.1 indicates moderate disease activity while DAS28-ESR >5.1 indicates high disease activity [12]. Health assessment questionnaire disability index (HAQ-DI) score [13] that reflect the functional status in adults with arthritis was recorded.

The anti-HCV treatment was also reviewed. A total of 46 patients received Direct Antiviral Drugs by a fixed-dose combination of Daclatasvir 60 mg and Sofosbuvir 400 mg once-daily for a 12-weeks period in Specialized Medical Hospital. While the other 9 patients received once weekly subcutaneous injection of Pegylated Interferon alfa-2a 180 mcg SC plus weight dependent ribavirin for 48 weeks in Mansoura International Hospital. The weight dependent ribavirin dose: 1000 mg/day for patients weighing < 75 kg and 1200 mg/day for those weighing >75 kg.

The laboratory data collected included the assessment of ESR level, C-reactive protein (CRP) level, ACPA titer, RF titer, complete blood count and serum glutamic pyruvic transaminase (SGPT) level.

The EULAR response criteria were used to evaluate the of RA response. The EULAR response criteria incorporate both the level of absolute disease activity and the extent of change in disease activity.

RA response were classified as a good response if DAS28 is ≤ 3.2 and has decreased by > 1.2, a moderate response if DAS28 is ≤ 3.2 and has decreased > 0.6 and ≤ 1.2, or if DAS28 is ≤ 5.1 and > 3.2 and has decreased > 0.6, or if DAS28 is > 5.1 and has decreased > 1.2 [14]. In the present study the RA patients showed good or moderate response were grouped together as responders.

Prior to the start of the antiviral treatment and 12 weeks after termination of therapeutic regimen for HCV, all the clinical and laboratory parameters of the studied subjects were taken from their medical records.

Statistical Analysis

Data analysis was done using SPSS software Version 26.0. Continuous normally distributed data were expressed as mean ±SD and compared using Student's t- test while continuous variables with abnormal distribution were compared using Mann-Whitney U test and presented as median and interquartile range [IQR]. The 95% confidence interval (CI) was calculated for the difference of mean DAS28-ESR between pre- and post-treatment. Categorical data were expressed as number and percentage using chi square test. Regression analysis was conducted to identify factors that can predict control of RA activity. The statistical significance was determined if p<0.05.

RESULTS

1.1 General Characteristics of the Patients

A total of 55 chronic HCV patients with RA were enrolled in the study, 46 females and 9 males. The age of the patients ranged between 27 and 62 years with the mean ±SD of 42.9 ±9.9 years. The duration of RA ranged from one to 32 years (median=10 and IQR=13). Regarding the current RA treatment, 100% of the patients were on hydroxychloroquine, 63.6% on sulfasalazine, 63.6% on corticosteroids, and 36.4% on biological therapy (etanercept).

1.2 Polymerase chain reaction (PCR) Evaluation at Pre- and Post- HCV Treatment

At pretreatment evaluation, PCR was positive in all patients. However, the post-treatment evaluation of PCR showed that among the 55 patients with concomitant chronic HCV infection and RA, 46 (83.6%) patients achieved sustained virologic response 12-weeks after treatment (SVR12) by direct acting antiviral therapy while the other 9 (16.4%) patients were still PCR +ve after 12 weeks of termination of interferon and ribavirin based treatment **(Figure 1)**.

1.3 Comparison of RA Activity Parameters between Pre- and Post- oral HCV Treatment

The parameters of RA activity were compared between the pre- and post-oral HCV treatment for patients who achieved SVR12 and were demonstrated in **Table 1**. The duration of morning stiffness showed significant improvement at the post-treatment evaluation (p <0.001). The frequency of the presence of the subcutaneous nodules was significantly decreased from 56.5% at pretreatment to 15.2% after achievement of SVR12 (p<0.001).

Concerning the DAS28-ESR status, among the HCV patients with RA, the frequency of high disease activity was decreased from 34.8% at pretreatment to 4.3% after achievement of SVR12 and, moreover, while none of the patients were in remission at pretreatment evaluation, 34.8% of the patients were in remission state after achievement of SVR12. This change of the activity status was significant (p<0.001) **(Table 1)**. In addition, the DAS28-ESR was decreased from 4.21 ±1.23 at the pretreatment to 3.13 ±1.23 after achievement of SVR12. This difference was significant (95% CI of 0.61 to 1.54, p <0.001) **(Table 1 and Figure 2)**. The HAQ-DI score showed significant improvement after achievement of SVR12 in comparison to the pre-oral HCV treatment (p<0.001) **(Table 1)**.

Similarly, the ESR and CRP levels showed significant improvement after achievement of SVR12 compared to the pretreatment evaluation (p<0.001). The serum SGPT level was significantly decreased from 107.0 ±33.1 at the pretreatment to 47.0 ±20.6 after achievement of SVR12 (p<0.001) **(Table 1)**.

1.4 Regression Analysis for Factors Predict Responders among the RA patients

The present study, among the patients who achieved SVR12, 35 RA patients (76.1%) achieved the EULAR criteria for response of RA (responders) while 11 patients did not achieve the EULAR response criteria despite that the DAS28-ESR score is decreased in these compared to the pretreatment values. The linear regression analysis was played to explore the factors that may predict the achievement of the EULAR response criteria. According to the regression analysis, attainment of SVR12 and pretreatment viral load strongly predicted the achievement of EULAR response criteria for improvement of disease activity **(Table 2)**.

Table 1: Comparison of the clinical features, RA activity score, HAQ-DI, and laboratory parameters between pre- and post-oral HCV treatment in the 46 patients who achieved SVR12

	Pretreatment	After achieving SVR12	p
Duration of morning stiffness (minutes) (median [IQR])	**65 [56.3]**	**22.7 [38.3]**	**<0.001**
Subcutaneous nodules (n, %)	**26, 56.5%**	**7, 15.2%**	**<0.001**
Neuropathy (n, %)	**26, 56.5%**	**25, 54.3%**	**0.834**
Vasculitis (n, %)	**2, 4.3%**	**0, 0%**	**0.153**
Fibromyalgia syndrome (n, %)	**24, 52.2%**	**23, 50.0%**	**0.835**
Sjogren Syndrome (n, %)	**9, 19.6%**	**4, 8.7%**	**0.135**
Trigger finger (n, %)	**4, 8.7%**	**3, 6.5%**	**0.694**
Arthralgia (n, %)	**46, 100%**	**21, 45.7%**	**<0.001**
Arthritis (n, %)	**46, 100%**	**15, 32.6%**	**<0.001**
DAS28-ESR (mean ±SD)	**4.21 ±1.23**	**3.13 ±1.23**	**<0.001**
Activity grade (n, %):			
Remission	**0, 0%**	**16, 34.8%**	**<0.001**
Low activity	**18, 39.1%**	**12, 26.1%**	
Moderate activity	**12, 26.1%**	**16, 34.8%**	
High activity	**16, 34.8%**	**2, 4.3%**	
HAQ-DI score (median [IQR])	**1.55 [1.13]**	**1.00 [1.05]**	**<0.001**
Hemoglobin concentration (mean ±SD)	**10.9 ±1.4**	**11.8 ±1.2**	**0.003**
RBCs count (million cells / mm^3) (mean ±SD)	**4.5 ±0.7**	**4.7 ±0.6**	**0.043**
WBCs count (thousand cells / mm^3) (mean ±SD)	**6.2 ±1.9**	**6.9 ±1.8**	**0.062**
Platelets count (thousand cells / mm^3) (mean ±SD)	**207.6 ±86.9**	**235.5 ±92.8**	**0.140**
ESR 1st hour (mm) (median [IQR])	**39.5 [56.3]**	**20.5 [17.3]**	**<0.001**
CRP (mg/dl) (median [IQR])	**18.0 [39.0]**	**11.5 [11.0]**	**<0.001**
SGPT (mean ±SD)	**107.0 ±33.1**	**47.0 ±20.6**	**<0.001**

RA, rheumatoid arthritis; HCV, hepatitis c virus; CRP, C-reactive protein; DAS, diseases activity score; ESR, erythrocyte sedimentation rate; HAQ-DI, health assessment questionnaire disability index; IQR, interquartile range, SVR 12, sustained virological response 12-weeks; RBCs, red blood cells; SGPT, serum glutamic-pyruvic transaminase; WBCs, white blood cells.

Table 2: Regression analysis to explore the factors that may predict the achievement of the EULAR response criteria

	Unstandardized Coefficients		Standardized Coefficients		
	B	Std. Error	Beta	t	Sig.
(Constant)	3.294	1.326		2.483	0.024
Age	-0.028	0.044	-0.230	-0.632	0.536
Sex	0.855	0.684	0.261	1.250	0.229
Duration of RA	0.083	0.054	0.604	1.534	0.145
Sulfasalazine	-0.417	0.388	-0.170	-1.074	0.299
Steroids	0.723	0.430	0.289	1.679	0.113
Biologicals	-0.339	0.490	-0.104	-0.693	0.498
Viral load at pretreatment evaluation	9.76×10^{-10}	0	0.444	2.376	0.026
Achieving SVR12	1.790	0.389	0.715	4.598	<0.001

EULRA, European League Against Rheumatism; RA, rheumatoid arthritis; SVR 12, sustained virological response 12-weeks.

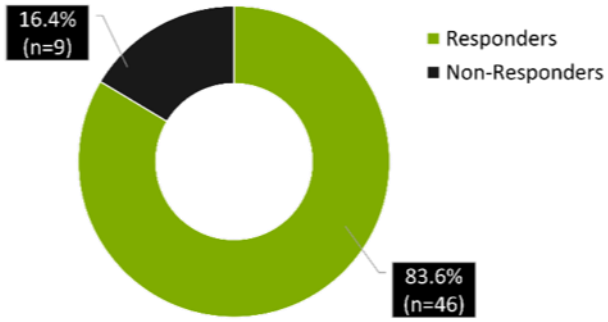

Figure (1): Frequency of patients who achieved SVR12.
Abb: SVR12, sustained virological response 12-weeks

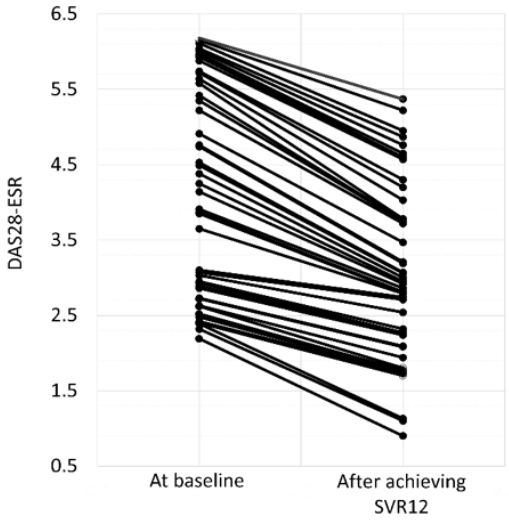

Figure (2): Paired scatterplot for DAS28-ESR at pretreatment and after achieving SVR12.

DISCUSSION

HCV infection is a serious health issue in Egypt, as it has one of the highest prevalence rates worldwide. The co-morbidity of RA and HCV infection can lead to substantial impact on the clinical outcomes of RA. Patients with comorbidity of RA and HCV infection are likely to have higher RA activity scores. Accordingly, it is hypothesized that eradication of HCV infection may improve disease activity in patients with comorbidity of RA and HCV infection. This study aimed to assess the potential impact of eradication of HCV on RA disease activity in patients with comorbidity of RA and HCV infection.

The major findings of this study include (a) DAS28-ESR score and status was significantly improved after achievement of SVR12; (b) while none of the patients with RA were in remission at the pretreatment evaluation, 34.8% of the RA patients were in remission state 12 weeks after achievement of SVR12 and (c) The regression analysis revealed that the achievement of SVR12 and pretreatment viral load strongly predicted the achievement of EULAR response criteria for improvement of disease activity.

In the present study, among the 55 patients with concomitant chronic HCV infection and RA, 46 (83.6%) patients achieved SVR12 after oral-HCV treatment for 12 weeks while only 9 (16.4%) patients were still PCR +ve after 12 weeks of termination of interferon and ribavirin based treatment.

In the present study, the successful treatment of chronic HCV had been associated with significant improvement of the RA activity. In this regard, the DAS28-ESR was significantly decreased after achievement of SVR12 compared to the pretreatment values of DAS28-ESR. In addition, among the HCV patients with RA, the frequency of high disease activity was decreased from 34.8% at pretreatment evaluation to 4.3% after achievement of SVR12 and, moreover, while none of the patients were in remission at pretreatment evaluation, 34.8% of the patients were in remission state post SVR12.

In addition, the clinical and laboratory markers of RA activity showed significant improvement post SVR12 in comparison to the pretreatment values including duration of morning stiffness, presence of subcutaneous nodules, CRP serum level. In addition, the improvement of activity markers was accompanied by improvement in the HAQ-DI score. The results of the current study were in consistency with the findings reported by the study of Lashen et al [15]. That study prospectively enrolled 65 patients with RA and HCV and found that SVR12 was achieved in 90.8% patients and was accompanied by a significant decline of RA activity. The study also reported that after SVR12, the DAS28 score showed significant reduction from that at the baseline in 79.9% patients. Moreover, a significant decrease in the mean levels of ESR and CRP after achieving an SVR12 was observed. The anti-rheumatic drugs were stepped-down in many patients as the RA activity had improved. In this regard, the number of patients who intake corticosteroids were reduced significantly from 27.1% patients pre-HCV treatment to 6.8% patients post-HCV treatment.

The results of the present study agree with the findings of a Japanese study that assessed the effectiveness of treatment in HCV infection patients with concomitant rheumatic diseases. That study included 2314 HCV infection patients with concomitant rheumatic diseases, including 11 patients with concomitant RA. Regarding RA patients, disease activity was measured at the baseline as well as at the end of the study using the simplified disease activity index (SDAI). The study reported that, with HCV elimination, the SDAI showed a median of 7.47 decline associated with a decline in RF level from the baseline level without elevating the dose of anti-rheumatic drugs [16]. In that study, the patients demonstrated improvement of the RA activity parameters without re-enforcement of the immunosuppressive drugs and none of the patients showed clinical deterioration. The study concluded that HCV elimination per se seems to contribute to the improvement of the activity of rheumatic diseases including RA.

The findings of the current study is also in agreement with the findings of a previous case report of a 78 years old female patient from Japan who had chronic HCV infection along with mixed cryoglobulinemia and RA who was referred for treatment of chronic HCV infection [17]. The RA diagnosis was based on the presence of typical erosions in the hands in plain radiography. At baseline evaluation, the DAS28-ESR was 6.6. A power Doppler (PD) ultrasound examination of the hands of the patient showed tenosynovitis of the extensors and active synovitis. After treatment, the patient achieved DAS28-ESR remission and showed rapid improvement of her arthritis as well as a SVR at 12 weeks. The study concluded that successfully treating HCV infection is associated with improvement of RA clinical features and diminished PD signals, indicating that treating HCV could be advantageous for treatment of RA.

It seems reasonable that achieving SVR12 is associated with significant improvement of the RA activity. In support to this concept, several previous studies reported that concomitant chronic HCV infection in RA patients is associated with worse disease activity in comparison to matched patients with RA alone [7,18,19]. The study of Patel et al. [7] showed that RA patients with comorbidity of HCV infection had higher DAS28 scores than RA patients without HCV infection and these patients had greater tender and swollen joint counts and higher global patient assessment score, the components that are incorporated in the DAS28 formula. In support to these observations, numerous previous studies stated that patients with SLE or psoriasis were similarly improved, but sometimes worsened, disease activity following treatment of the chronic HCV infection [20,21,22].

It had been suggested that the higher DAS28 in HCV-positive patients is driven primarily by the greater inflammatory burden due to co-existence of both diseases. Chronic HCV replication is associated with chronic generation of antigens in the circulation leading to chronic stimulation of the immune system. The higher viral load and the persistent stimulation may lead to proliferation and clonal expansion of the inflammatory cells with the generation of proinflammatory mediators that induce and augment inflammation [23]. The finding that achieving SVR12 is associated with improvement of disease activity emphasizes this concept. By HCV infection elimination, it is likely that this pathway is obliterated leading to decline in the proinflammatory mediators release, resulting in subsiding of the ongoing inflammatory process [24,25,26].

The results of regression analysis revealed that the SVR12 and pretreatment viral load strongly predicted the achievement of EULAR response criteria for improvement of disease activity. This finding is in agreement with the finding of a previous study that reported that the achievement of

HCV clearance in addition to baseline viral load were the independent predictors of improvements of RA [15].

Although the pathophysiology of RA is not fully understood, there is some evidence that viral infections may be a factor. Because of HCV's lymphotropic properties, it causes the host's immune system to become chronically activated resulting in proliferation of lymphocytic cells and production of immune complexes [18]. It had been found that levels of RF and anti-CCP antibodies are increased in HCV-positive subjects [27]. An abnormal defensive immunological response could be developed by the host. Accordingly, HCV infection may increase susceptibility and aggravate autoimmune diseases including RA [28]. A previous study found a significant association of development of RA and HCV infection [4]. This prompts the question of whether treating HCV can improve RA activity. Our study revealed decreased RA activity in HCV treated patients. The laboratory data such as viral load and persistent virologic response were correlated with RA activity, which is the current study's main strength. To the best of our knowledge, this correlation was not assessed previously.

Limitations of the present study include the small sample size and the relatively short follow-up. Future multicenter studies with larger sample size are advocated to introduce more generalizable results. A prospective longitudinal study with a longer follow-up period of RA activity can better address whether the improvements in the disease activity is maintained following elimination of HCV infection. In addition, assessing RA activity in the joints by musculoskeletal ultrasound was not performed in the current work.

In conclusion, the results of our study showed that elimination of HCV is associated with significant improvement in RA activity in chronic HCV infection patients with concomitant RA.

Conflict of interest: None to declare

Funding: None to declare

REFERENCES

1. **Polaris Observatory HCV Collaborators**. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. *Lancet Gastroenterol Hepatol*. 2017 Mar;2(3):161-176.
2. **El-Zanaty F, Way A.** Egypt Demographic and Health Survey 2008. Cairo: Ministry of Health, El-Zanaty and Associates and Macro International. 2009. p. 431
3. **El-Zanaty F, Way A.** Egypt health issue survey. Ministry of Health and Population. Cairo, Egypt. 2015.
4. **Su FH, Wu CS, Sung FC, Chang SN, Su CT, Shieh YH, et al.** Chronic hepatitis C virus infection is associated with the development of rheumatoid arthritis: a nationwide population-based study in Taiwan. *PLoS One*. 2014 Nov 21;9(11):e113579.
5. **Cacoub P, Comarmond C.** New insights into HCV-related rheumatologic disorders: A review. *J Adv Res*. 2017;8(2):89-97.
6. **Lin KM, Chen WM, Tung SY, Wei KL, Shen CH, Chang TS, et al.** Prevalence and predictive value of high-positive rheumatoid factor and anti-citrullinated protein antibody levels in nonarthritic patients with chronic hepatitis C infection. *Int J Rheum Dis*. 2019 Jan;22(1):116-120.
7. **Patel R, Mikuls TR, Richards JS, Kerr G, Cannon GW, Baker JF.** Disease characteristics and treatment patterns in veterans with rheumatoid arthritis and concomitant hepatitis C infection. *Arthritis Care Res (Hoboken)*. 2015 Apr;67(4):467-74
8. **Burton MJ, Curtis JR, Yang S, Chen L, Singh JA, Mikuls TR, et al.** Safety of Biologic and Nonbiologic Disease-modifying Antirheumatic Drug Therapy in Veterans with Rheumatoid Arthritis and Hepatitis C Virus Infection. *J Rheumatol*. 2017 May;44(5):565-570.
9. **Liao TL, Hsieh SL, Chen YM, Chen HH, Liu HJ, Lee HC, et al.** Rituximab May Cause Increased Hepatitis C Virus Viremia in Rheumatoid Arthritis Patients Through Declining Exosomal MicroRNA-155. *Arthritis Rheumatol*. 2018 Aug;70(8):1209-1219.
10. **Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al.** 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2010 Sep;62(9):2569-81.
11. **Li HC, Lo SY.** Hepatitis C virus: Virology, diagnosis and treatment. *World J Hepatol*. 2015;7(10):1377-1389.
12. **Aletaha D, Ward MM, Machold KP, Nell VP, Stamm T, Smolen JS.** Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. *Arthritis Rheum*. 2005 Sep;52(9):2625-36.
13. **Bruce B, Fries JF.** The Stanford Health Assessment Questionnaire: dimensions and practical applications. *Health Qual Life Outcomes*. 2003;1:20.
14. **Fransen J, van Riel PL.** The Disease Activity

Score and the EULAR response criteria. *Rheum Dis Clin North Am*. 2009 Nov;35(4):745-57, vii-viii.

15. **Lashen SA, Metawea MI, Shaaban A.** Direct antiviral drugs in the treatment of hepatitis C-infected rheumatoid arthritis Egyptian cohort: safety and clinical impact. *Eur J Gastroenterol Hepatol*. 2021 Dec 1;33(1S Suppl 1):e239-e246.
16. **Kida T, Umemura A, Kaneshita S, Sagawa R, Inoue T, Toyama S, et al.** Effectiveness and safety of chronic hepatitis C treatment with direct-acting antivirals in patients with rheumatic diseases: A case-series. *Mod Rheumatol*. 2020 Nov;30(6):1009-1015.
17. **Koga T, Kawashiri SY, Nakao K, Kawakami A.** Successful ledipasvir + sofosbuvir treatment of active synovitis in a rheumatoid arthritis patient with hepatitis C virus-related mixed cryoglobulinemia. *Mod Rheumatol*. 2017 Sep;27(5):917-918
18. **Ferri C, Ferraccioli G, Ferrari D, Galeazzi M, Lapadula G, Montecucco C, et al.** Safety of anti-tumor necrosis factor-alpha therapy in patients with rheumatoid arthritis and chronic hepatitis C virus infection. *J Rheumatol*. 2008;35(10):1944-9.
19. **Ramos-Casals M, Jara LJ, Medina F, Rosas J, Calvo-Alen J, Mañá J, et al.** Systemic autoimmune diseases co-existing with chronic hepatitis C virus infection (the HISPAMEC Registry): patterns of clinical and immunological expression in 180 cases. *J Intern Med*. 2005 Jun;257(6):549-57.
20. **Enomoto M, Tateishi C, Tsuruta D, Tamori A, Kawada N.** Remission of Psoriasis After Treatment of Chronic Hepatitis C Virus Infection With Direct-Acting Antivirals. *Ann Intern Med*. 2018 May 1;168(9):678-680.
21. **Damiani G, Franchi C, Pigatto P, Altomare A, Pacifico A, Petrou S, et al.** Outcomes assessment of hepatitis C virus-positive psoriatic patients treated using pegylated interferon in combination with ribavirin compared to new Direct-Acting Antiviral agents. *World J Hepatol*. 2018 Feb 27;10(2):329-336.
22. **Nakamura H, Fujieda Y, Yasuda S, Nakai M, Atsumi T.** Remission of Nephrotic Syndrome After Therapy for Chronic Hepatitis C Virus Infection in a Patient With Systemic Lupus Erythematosus. *Ann Intern Med*. 2018 Sep 4;169(5):352-353.
23. **Cacoub P, Poynard T, Ghillani P, Charlotte F, Olivi M, Piette JC, et al.** Extrahepatic manifestations of chronic hepatitis C. MULTIVIRC Group. Multidepartment Virus C. *Arthritis Rheum*. 1999 Oct;42(10):2204-12.
24. **Barkhuizen A, Rosen HR, Wolf S, Flora K, Benner K, Bennett RM.** Musculoskeletal pain and fatigue are associated with chronic hepatitis C: a report of 239 hepatology clinic patients. *Am J Gastroenterol*. 1999 May;94(5):1355-60.
25. **Buskila D.** Hepatitis C-associated arthritis. *Curr Opin Rheumatol*. 2000 Jul;12(4):295-9.
26. **Lormeau C, Falgarone G, Roulot D, Boissier MC.** Rheumatologic manifestations of chronic hepatitis C infection. *Joint Bone Spine*. 2006 Dec;73(6):633-8.
27. **Himoto T, Masaki T.** Extrahepatic manifestations and autoantibodies in patients with hepatitis C virus infection. *Clin Dev Immunol*. 2012;2012:871401.
28. **Palazzi C, D'Amico E, D'Angelo S, Gilio M, Olivieri I.** Rheumatic manifestations of hepatitis C virus chronic infection: Indications for a correct diagnosis. *World J Gastroenterol*. 2016 Jan 28;22(4):1405-10.

To cite:
Abd El Ghafar, D., Elzayyadi, I., Abd Allah, A., Gaafar, S., Bakr, E. Impact of HCV Eradication on Rheumatoid Arthritis Activity in Rheumatoid Arthritis Patients with Concomitant HCV Infection. *Zagazig University Medical Journal*, 2023; (1440-1447): -. doi: 10.21608/zumj.2023.182913.2706