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Safety and efficacy of direct-acting antiviral agents on extra-hepatic manifestations of chronic hepatitis C virus

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Abstract: Background: Data on outcomes of direct-acting antiviral agents (DAAs) in hepatitis C virus (HCV)-related extrahepatic manifestations (EHMs) is scarce. We aimed to assess the safety and efficacy of sofosbuvir (SOF)-based regimens in HCV-related EHMs.

Methods: 100 patients with HCV-related EHMs were recruited from three tertiary care centers in Egypt. SOF-based regimens included 35 patients who received SOF-based DAAs combination for 3 months, 23 patients who received SOF plus ribavirin (RBV) for 6 months, and 42 patients who received pegylated-interferon (INF)/RBV plus SOF for 3 months. The virological response was assessed by the sustained virological response (SVR12), clinical response (CR) included resolution of symptoms and signs of EHMs, and the immunological response was assessed by the disappearance of cryoglobulins at end of treatment and SVR12.

Results: Overall end of treatment virological, complete CR, and immunological responses were 96%, 95%, and 92 % respectively, while SVR12, CR, and immunological responses were 92%, 89%, and 69.2% among regimens. CR was higher in DAAs combinations without RBV (97.1%), less for IFN-based regimen (85.7%), and the least with SOF+ RBV (82.6%). Recurrence and adverse events were higher in SOF+RBV.

Conclusion: Successful HCV eradication by DAAs was associated with clinical and immunological improvement of EHMs. DAAs combination regimen was safer and more effective in achieving SVR and CR.

Keywords: *Direct-acting antivirals (DAAs), Extra-hepatic manifestations (EHMs), Sustained virological response (SVR), Hepatitis C virus (HCV), Clinical response (CR).*

Introduction

Hepatitis C virus (HCV) affects many organs other than the liver and can cause immune abnormalities resulting in autoimmunity, which may be involved in the development of extrahepatic manifestations (EHMs) [1]. Nearly 75% of patients with HCV infection experience some type of EHMs, classified into immune-related and inflammatory-related EHMs [2]. The main extrahepatic manifestations of HCV infection are mixed cryoglobulinemia vasculitis (MCV), affecting about 40–50% of chronic HCV-infected patients [3], glomerulonephritis in 20%–35%, auto-antibodies production (cryoglobulins, rheumatoid factor (RF), antinuclear, anticardiolipin, anti-thyroid and anti-smooth muscle antibodies), arthralgia/myalgia, skin disorders, and other manifestations including immune thrombocytopenia, depression, sicca syndrome, lichen planus, thyroid dysfunction, and fatigue [4].

Traditionally, antiviral therapy for HCV included pegylated interferon and ribavirin (pegIFN+ RBV) which led to HCV suppression and improve HCV-MCV when sustained virological response (SVR) is achieved. However, IFN-based regimens can increase the risk for the development of autoimmune diseases, lower SVR rates, and other adverse effects [5].

Direct-acting antivirals (DAAs) are major developments in the treatment of HCV infection, with cure rates higher than 90% [6]. Throughout the development of DAAs, various combination therapies have been studied and used [7]. Long-term viral eradication with DAAs regimens is associated with a reduction in all-cause mortality, cardiovascular, metabolic, renal, and hematologic/oncologic complications, as well as improvement in quality of life. Improvement in extrahepatic outcomes is additional strong evidence to advocate treatment for all infected persons [8], however, data regarding the efficacy of interferon-free therapies in EHMs of HCV is only available from studies involving a relatively small number of patients [9]. This work aims to assess the safety and efficacy of different DAAs regimens including, sofosbuvir-based (SOF-based) regimens with or without IFN on extrahepatic manifestations of HCV in Egyptian patients who are a candidate for antiviral therapy.

Methods

Study population:

We prospectively enrolled 100 patients with different EHMs of HCV; these patients were a candidate for anti-viral therapy according to the HCV treatment protocol issued by the National Committee for Control of Viral Hepatitis, Ministry of Health and Population (MOHP), Cairo, Egypt. Patients were recruited from February 2015 to December 2016, and different DAAs regimens were used according to the availability and treatment protocol at that time.

Inclusion criteria included adults (18-70 years old), treatment naïve or IFN experienced chronic HCV with related EHMs and compensated chronic liver disease. Informed consent was taken from all patients and the study was approved by the institutional ethics committee. EHMs included hematologic diseases such as essential mixed cryoglobulinemia, renal diseases, autoimmune disorders such as thyroiditis, the presence of autoantibodies (cryoglobulins, rheumatoid factor, and antinuclear, anticardiolipin, anti-thyroid and anti-smooth muscle antibodies) and dermatologic conditions such as psoriasis, lichen planus and other HCV associated skin manifestations. Exclusion criteria included adult patients >70 years old, decompensated chronic liver disease, pregnant or nursing females, human immunodeficiency virus or active hepatitis B virus co-infection, post-liver transplantation, co-existence of autoimmune diseases, chronic use of corticosteroids with dose > 15 mg per day, hypersensitivity to recommended therapy, co-morbid condition as poorly controlled diabetes, ischemic cardiovascular disease, platelets count <50,000/μL, and IFN deferring criteria [10].

After fulfilling the inclusion criteria, three groups were assigned according to the availability of DAAs regimens at the time of recruitment:

Group A: 35 patients who received DAAs combination without ribavirin (RBV) for 3 months; 16 patients received sofosbuvir (SOF) (400 mg) + simeprevir (SIM) (150 mg) and 19 patients received SOF (400 mg) + daclatasvir (DAC) (60 mg).

Group B: 23 patients who received SOF (400 mg) and weight based RBV; 1000 mg [<75 kg] to 1200 mg [≥75 kg] for 6 months.

Group C: 42 patients who received weekly subcutaneous pegylated-IFN, weight-based RBV 1000 mg [<75 kg] to 1200 mg [≥75 kg] and SOF (400 mg) for 3 months.

Baseline assessment:

History taking and clinical assessment emphasized extrahepatic manifestations such as vasculitis, cutaneous manifestations such as psoriasis and lichen planus, rash, purpura, lower limb edema, and dry eye in sicca syndrome.

Laboratory assessment included complete blood count, liver biochemical profile, kidney function, viral markers (HCV Ab, HCV PCR quantitative, HBsAg), alfa fetoprotein (AFP), thyroid-stimulating hormone (TSH), free T3, T4, and markers for diagnosis of EHMs, including immunological markers as cryoglobulins, C3 and C4, autoantibodies as antinuclear antibody (ANA), RF, antithyroglobulin and antiplatelet antibodies. Abdominal ultrasound was done to examine the liver for the presence of cirrhosis and its complications, and an examination of the kidneys to detect renal affection. Transient elastography for measuring liver stiffness was done for all patients, the degree of fibrosis was determined according to the following cut-off values; **≤** 7 Kpa= F0-F1, 8.8 Kpa= ≥ F2, 9.6 Kpa= ≥ F3, 14.6 Kpa= F4 [11].

Diagnosis of extrahepatic manifestations:

Various HCV-related EHMs were diagnosed based on clinical presentation, serological investigations, and tissue biopsy. Dermatological manifestations were diagnosed based on clinical examination by a dermatologist together with skin biopsy on suspected cases [12], glomerulonephritis was diagnosed based on urine analysis findings, ultrasonographic features of kidney affection, autoimmune serum markers (C3, C4, cryoglobulins, ANA) and renal biopsy [13], thyroid dysfunction was diagnosed based on thyroid hormones, thyroid ultrasound, and antithyroglobulin antibodies [14], and finally, HCV associated thrombocytopenia was diagnosed by the presence of thrombocytopenia in peripheral blood film and antiplatelet antibodies [15].

Follow up:

Follow-up was done during antiviral therapy, at the end of treatment, and 12 weeks after the stoppage of treatment. Follow-up included evaluation of patient compliance, virological response, clinical, and laboratory assessment of extrahepatic manifestations, and drug side effects. Virological, immunological, and clinical responses were evaluated: the virological response was defined as negative PCR of HCV at end of treatment and week 12 after treatment (SVR 12). The clinical response included complete response (CR): complete disappearance or remarkable improvement of baseline clinical features, partial response (PR): the resolution of at least half of the base-line symptoms and no response (NR): patients who didn't meet the previous criteria were categorized as non-responders. The immunological response was assessed by the normalization of cryoglobulins [16].

Statistical analysis

Data have been coded and entered using the statistical package SPSS version 15. Data were summarized using mean, standard deviation, and range (minimum and maximum) for quantitative variables and number and percent for qualitative variables. Comparisons between groups were done using the Chi-square test and fisher's exact test for qualitative variables while the independent sample T-test for normally distributed quantitative variables and nonparametric Mann Whitney test were used for quantitative variables which are not normally distributed. P values less than or equal to 0.05 were considered statistically significant. Logistic regression to control the effect of other variables that are associated with treatment response was done.

Results

Baseline characteristics of patients with HCV– related extrahepatic manifestations:

A total of one hundred patients with HCV-related EHMs received different regimens of DAAs therapy, the mean age was 52 years (range 22–69 years), and 58% were males. Ninety-one (91%) of HCV patients were treatment-naive to previous INF-based therapy. HCV-related EHMs included 53 % have skin diseases (28% psoriasis, 25% lichen planus), 10% glomerulonephritis (all are of membranoproliferative type), 11% hyperthyroidism, 9%

thrombocytopenia, 7% have autoantibodies (5% ANA, 2% RF), 5% monoclonal gammopathy, 3% arthralgia, and 2% necrolytic acral erythema. Cryoglobulins were present in 13 % of patients. The mean LSM±SD was 13.5±7.6 Kpa as detected by transient elastography, 36% of patients had compensated cirrhosis (Child A-class). Baseline characteristics and laboratory data of the study population are summarized in **Table 1**.

Treatment by different antiviral therapy

Different SOF-based regimens were given for chronic HCV patients with different forms of EHMs, the choice of the treatment regimens was given according to the contraindication and interactions with different DAAs as shown in **Table 2.**

Virological, clinical, and immunological responses after antiviral therapy

Virological response:

The overall end of therapy virological response and SVR 12 were 96 and 92% respectively. Higher SVR 12 was observed among patients who received DAAs combinations 97.1% compared to 92.8% in IFN based and 82.6% in DAAs+RBV regimens respectively (P= 0.0001) as shown in **Table 3**.

Based on the multiple logistic regression model, the use of DAAs combination was associated with higher rates of virological response (odds ratio= 2.33), while patients with higher platelets and ALT levels showed a higher rate of virological response (odds ratio=1.8, 1.98 respectively) as shown in **Table 4**.

Clinical and immunological response:

The overall complete clinical response of EHMs among the whole cohort at end of treatment and SVR12 was 95 and 89 % respectively. Complete clinical response was significantly higher in patients who received DAAs combination at end of treatment and SVR 12, 100% and 97.1% respectively, compared to those who received other regimens, the end of treatment and SVR 12 were 95.2% and 85.7% for INF-based regimen and were 90% and 82.6% for SOF+RBV regimen (P=0.0002, 0.03) respectively as shown in **Table 3**.

In DAAs combination, CR and PR were observed with the start of week 4; 17.1% and 74.3 % respectively, CR progressed till the end of therapy to 100 %, but declined in SVR12 to be 97.1%, on the other side, in SOF+RBV regimen CR and PR were 4.3% and 82.6% respectively at week 4, CR progressed till the end of therapy to 90%, but declined in SVR12 to be 82.6%, and finally in INF-based regimen CR and PR were 4.8% and 78.6% respectively at week 4, CR progressed till the end of therapy to 95.2%, but declined in SVR12 to be 85.7%.

Recurrence of EHMs was the least among patients who received DAAs combination (2.9%), compared to 17.4% and 14.3% for SOF/RBV and IFN-based regimens respectively (P=0.03) as shown in table 3. Clinical recurrence was significantly higher in patients who didn't achieve SVR 12 (P=0.0029) as shown in **Figure 1.** As regards immunological response, there was a significant decrease in serum level of cryoglobulins after antiviral therapy, 12/13 of patients with positive cryoglobulins were negative (92.3%) at end of treatment, as shown in **Table 3**. However, at SVR 12 recurrence of cryoglobulins occurred in three patients in all studied groups as shown in **Table 1**.

Adverse effects of HCV antiviral therapy in studied groups

Adverse effects were significantly higher in a group of patients who received DAAs and RBV than in other groups. The commonly observed adverse effects were anemia (26%), hyperbilirubinemia (17.3%) with SOF+RBV, photosensitivity (5.7%) with SOF/SIM, on the other hand, IFN-related adverse effects were anemia (9.5%) and neutropenia (2.3%).

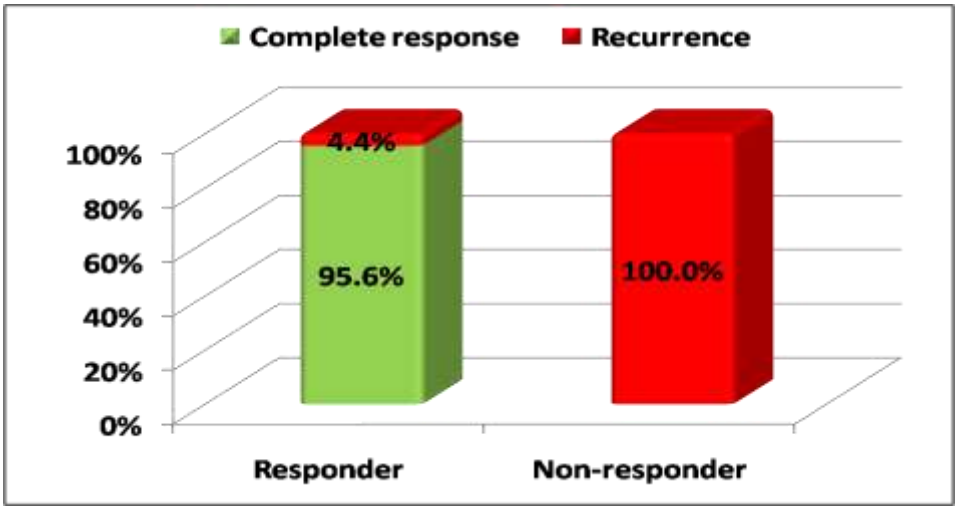

Figure (1): Clinical response versus virological response to antiviral treatment among chronic HCV patients with extrahepatic manifestations (N=100).

Table (1): Baseline characteristics, laboratory data, fibrosis stages, and types of extrahepatic manifestations among chronic HCV patients and follow up labs at SVR12 (n=100)

Variables	**Mean±SD**	**Range**	**Mean± SD at SVR12**	**Mean difference at SVR12**	**p-value**
Age (years)	52.3±10.8	22.0–69.0			
*Sex (n, %) Male/Female	85/15				
*Treatment with IFN (n, %) Naïve Experienced	91 9	91.0 9.0			
HCV RNA (x10³/mL)	123.4±90.6	3.3–15547.5			
Hemoglobin (gm/dL)	12.5±1.4	10.2–15.0	12.1±1.3	-0.400	**<0.0001**
Total leukocytic count (/cmm)	5.5±1.2	3.6–8.0	4.7±0.6	-0.800	0.03
Platelets (x10³/mL)	192.9±77.6	87.0–376.0	195±81.6	2.1	0.8
ALT (up to 40 IU/L)	53.1±19.9	25.0–98.0	34.7±30.1	-18.4	**<0.0001**
AST (up to 40 IU/L)	54.7±20.6	17.0–89.0	44.7±29.6	-10.000	0.06
Total bilirubin (mg/dL)	1.2±0.4	0.5–1.9	1.17±0.6	-0.030	0.6
INR	1.2±0.1	1.0–1.5	1.1±0.1	-0.100	0.01
Albumin (g/dL)	4.1±0.4	3.6–4.2	4.3±0.9	0.200	0.04
Creatinine (mg/dl)	0.91±1.3	0.5–2.4	0.7±0.3	-0.200	0.13
AFP (up to 10 ng/mL)	12.3±9.9	1.6–23	9.9±8.6	-2.400	0.06
TSH (up to 40 IU/L)	3.8±6.4	0.5–41.0	2.4±2.1	-1.4	0.03
LSM (Kpa)	13.5±7.6	4.6–48.2	12.7	-9.000	**<0.0001**
*Positive cryoglobulins	13	13	4	-	**0.003**

*Data were expressed as numbers and percentage

SD: standard deviation, ALT: alanine transaminase, AST: aspartate transaminase, INR: international normalization ratio, AFP: alfa fetoprotein, TSH: thyroid-stimulating hormone, LSM: liver stiffness measurements.

Table (2) : Different SOF-based regimens prescribed to HCV patients with different extrahepatic manifestations.

Extrahepatic Manifestations		**DAAs combination without RBV (N=35)**	**DAA+RBV (N=23)**	**IFN based (N=42)**
Psoriasis (n=28)		8 (22.8%)	8 (34.7%)	12 (28.5%)
Lichen Planus (n=25)		9 (25.7%)	5 (21.7%)	11 (26.1%)
Hyperthyroidism (n=11)		3 (8.5%)	4 (17.4%)	4 (17.4%)
Glomerulonephritis (n=10)		7 (20.0%)	1 (4.3%)	2 (4.8%)
Thrombocytopenia (n=9)		2 (5.7%)	3 (13.0%)	4 (9.5%)
Autoantibodies	**ANA (n=5)**	2 (5.7%)	0	3 (7.1%)
	RF (n=2)	0	0	2 (4.8%)
Monoclonal gammopathy (n=5)		2 (5.7%)	1 (4.3%)	2 (4.8%)
Arthralgia (n=3)		0	1 (4.3%)	2 (4.8%)
Necrolytic acral erythema (n=2)		2 (5.7%)	0	0

Data were expressed as numbers and percentages, and DAAs combinations included (SOF+SIM) or (SOF+DAC) without RBV.

ANA: antinuclear antibodies, DAAs: direct-acting antiviral agents, FR: rheumatoid factor, INF: interferon, RBV: ribavirin, SOF: sofosbuvir.

Table (3): Virological, biochemical, clinical, and immunological response (at end of treatment and SVR 12) of studied groups according to the treatment regimen.

Variables	DAAs combination (N=35)	DAAs+RBV (N=23)	IFN based (N=42)	P-value
Virological response:				
End of treatment:				
Responder	35 (100%) [a]	20(86.9%) [b]	41 (97.6%) [bc]	**0.007**
Non-responder	0 (0%)	3 (13.0%)	1 (2.3%)	
SVR 12:				
Responder	34 (97.1%) [a]	19 (82.6%) [b]	39 (92.8%) [bc]	**0.0001**
Non-responder	1 (2.9%)	4 (17.3%)	3 (7.14%)	
Biochemical response:				
Hb (gm/dL), mean±SD (range)	12.8±1.4 [a] (11.2–15.0)	10.5±0.7 [ab] (9.5–12.5)	11.9±0.9 [ac] (10.3–13.2)	0.21
PLT (x10^3), mean±SD (range)	201±77.6 [a] (120.0–390.0)	154.5±31.6 [b] (109.0–200.0)	311.9±62.9 [ac] (210.0–391.0)	**0.002**
T. bilirubin (mg/dL), mean±SD (range)	1.1±0.4 [a] (0.5–1.7)	1.7±0.3 [ab] (1.1–2.7)	0.8±0.3 [ac] (0.2–1.3)	0.71
ALT (up to 40 IU/L), mean±SD (range)	33.1±13.9 [a] (15.0–68.0)	67.2±20.5 [b] (30.0-88.0)	22.8±8.6 [bc] (10.0–40.0)	**0.0001**
AST (up to 40 IU/L), mean±SD (range)	34.7±17.6 [a] (17.0–69.0)	42.4±11.0 [ab] (25.0–68.0)	23.2±8.4 [ac] (14.0–34.0)	0.12
Creatinine(mg/dl), mean±SD (range)				
TSH (up to 4.5 µIU/L), mean±SD (range)	1.0±0.1 [a] (0.50–1.7)	1.1±1.1 [b] (1.0–1.7)	1.0±1.6 [bc] (0.9–1.9)	0.85
Immunological response:				
End of treatment:				
Cryoglobulins (N %)	2.5±1.3 [a] (0.7–7.0)	2.5±2.7 [b] (0.6–11.0)	2.3±2.3 [bc] (0.5–11.0)	**0.004**
Clinical response:				
End of treatment:				
CR	1 (2.9%) [a]	0 (0 **%)**[b]	0 (0%) [bc]	**0.005**
Recurrence	35 (100%) [a]	20 (90%) [b]	40 (95.2%) [bc]	
SVR-12:	0	3 (10%)	2 (4.7%)	**0.0002**
CR				
Recurrence	34 (97.1%) [a]	19 (82.6%) [b]	36 (85.7%) [bc]	
	1 (2.9%)	4 (17.4%)	6 (14.3%)	**0.03**

Independent t-test, Chi-square test N.B: Groups sharing the same letters are not significant.

ANOVA test &Fisher's Exact test, N.B: Groups sharing the same letters are not significant

* ALT: alanine transaminase, AST: aspartate transaminase, CR= Complete response, DAAs: direct-acting antiviral agents, FR: rheumatoid factor, Hb: hemoglobin INF: interferon, NR= No response, PLT: platelets, PR= Partial response, RBV: ribavirin, SOF: sofosbuvir, SVR: sustained virological response, TSH: thyroid-stimulating hormone.

Table (4): Association of independent variables with a virological and clinical response based on multiple logistic regression model.

Variable		**Virological response**	**Clinical response**	**P-value**
		Odds ratio	**Odds ratio**	
Age		1.0	1.0	0.3
Sex		0.9	1.0	0.07
IFN experience		0.7	0.4	0.1
Labs	**Hb**	1.0	0.9	0.32
	PLT	**1.8**	1.0	**0.003**
	Bilirubin	0.3	0.87	0.44
	AST	1.0	0.1	0.89
	ALT	**1.98**	0.9	**<0.0001**
	Albumin	0.9	0.65	0.46
	Baseline PCR	1.0	0.45	0.23
	Cryoglobulins	0.7	1.0	0.6
LSM		0.5	0.7	0.7
Type of EHM		1.0	1.0	0.12
Regimens	**DAAs combinations**	**2.33**	**1.9**	**0.005**
	SOF+RBV	1.0	0.1	0.44
	IFN+SOF+RBV	0.6	0.4	0.9
Virological response		----	**2.9**	**<0.0001**

ALT: alanine transaminase, AST: aspartate transaminase, DAAs: direct-acting antiviral agents, EHMs: extrahepatic manifestations, Hb: hemoglobin INF: interferon, LSM: liver stiffness measurements, PLT: platelets, RBV: ribavirin, SOF: sofosbuvir.

Discussion

With the introduction of DAAs for the treatment of chronic HCV, few Egyptian studies have assessed the effect of DAAs on EHMs related to HCV. Thus, we aimed to assess the safety and efficacy of different SOF-based regimens on different EHMs in Egyptian patients with chronic hepatitis C who are a candidate for antiviral therapy. The efficacy of antiviral therapy among HCV-related EHMs was assessed based on clinical response, virological response, and immunological response.

In our study**,** SVR12 was significantly higher in patients who received SOF-based DAAs combinations (97.1%) in comparison to IFN-based and SOF/RBV regimens (92.8%, 82.6%, respectively), indicating higher virological response to DAAs combinations than IFN-based or single DAA-based regimens. This reflects the more rapid

kinetic decline of the virus seen with DAAs [17]. This was consistent with Gragnani. et al. [18], who showed a rapid decrease of viremia in all patients who received DAAs, with eventual 100% SVR12, and with no viral breakthrough, unlike with IFN- based regimens. Moreover, compared to interferon-based antiviral therapy, there are substantial improvements in SVR rates with DAAs, with a shorter duration of therapy and fewer side effects [19].

In our study, the overall clinical response of EHMs among the whole cohort was 89 %, which was significantly related to the achievement of SVR 12. Clinical response was the best with DAAs combinations (97.1 %), followed by IFN-based regimens (85.7%) and least with SOF/RBV-based regimens (82.6%). The clinical and virological response was not affected by the type of EHMs as there was no significant increase in the type of EHMs among non-responders. Clinical recurrence of EHMs was observed in 11% of patients, after the stoppage of treatment, and was the least in patients who received DAAs combination (2.9%) compared to SOF/RBV-based regimens (17.4%) and IFN based regimen (14.3%). Clinical recurrence of EHMs was significantly higher in virological non-responders than in responders, indicating that the higher rates of SVR with the introduction of DAAs in clinical practice improve the extrahepatic manifestations dramatically. Concerning the safety of different DAAs regimens in our study, the DAAs combination regimen had fewer side effects causing better compliance of the patients to treatment. The different side effects encountered were anemia, neutropenia, photosensitivity, and hyperbilirubinemia, patients who received SOF based DAA combinations suffered from anemia (2.8%) and photosensitivity (5.7%) had a wider safety spectrum compared to SOF/RBV based regimen who suffered from anemia (26.0%) and hyperbilirubinemia (17.3%). These findings reflect the greater efficacy of DAAs combination regimens, achieving better clinical improvement of EHMs with lower recurrence rate and fewer side effects compared with the IFN-based or single DAAs regimens, that was reported by several studies [18, 20, 21], one study showed that the use of different sofosbuvir-based DAAs combinations is highly effective and safe for HCV-associated mixed cryoglobulinemic patients; the overall clinical response of vasculitis was 100%, on an intention-to-treat basis, with no difference in the outcomes in patients receiving specific DAAs combinations [18], compared to lower rate of clinical response observed with SOF/RBV for treatment of EHMs, complete clinical response was 87.5% at week 24 [21], regarding the efficacy of SOF/DAC regimen; the widely used antiviral therapy in Egypt, there is complete clinical response in 93.3% of patients with dermatological manifestations due to HCV, including hepatic pruritus, psoriasis and lichen planus [22].

Regarding immunological response, in our study 13 patients had positive cryoglobulins at baseline, while after antiviral therapy, 12 patients (92.3%) have complete cryoprecipitate clearance at end of treatment, however, at SVR 12 recurrence of cryoglobulins recurred in 3 (23%) cryo-positive patients. This was similar to previous studies reported [16, 23, 24], DAAs not only effectively and safely eradicate HCV, but also achieve some unexpected extrahepatic benefits compared to interferon-based therapy, such as the recovery of metabolic impairment and restoration of immunity dysfunction [25,26], they trigger a global rearrangement of innate immune signals and inflammatory pathways in patients with chronic hepatitis C [27]. The decrease in cryoglobulins was found to be beneficial for HCV-associated mixed cryoglobulinemia, as these patients can have complete resolution of symptoms of cryoglobulinemia [23]. However, some studies reported that the degree of immunologic activation still was present in nearly 50% of patients at the end of follow-up evaluation with both IFN and DAAs regimens. Although a possible explanation of this finding might be that B-cell clonal expansion continues expanding in a virus-independent fashion [28,29,30].

The limitation of our study is that we didn't do follow-up labs for all immunological markers including RF and ANA, which limited the wide diversity of different extrahepatic manifestations.

Conclusion:

In the era of DDAs, SVR 12 among HCV with extrahepatic manifestations was similar to those without extrahepatic manifestations. Clinical improvement of HCV-EHMs was related to SVR 12, and recurrence was associated with virological non-response. Different DAAs combinations without ribavirin were more effective in achieving virological, clinical, and immunological responses, with fewer adverse events than IFN-based and sofosbuvir/ribavirin regimens.

Declarations

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Availability of data and material: The data supporting the results are available from the corresponding author upon reasonable request.

Authors' contributions: Ahmed Abdelhalim: Conceptualization**,** Investigation, Methodology Yasmine Gaber Writing **-** original draft. Naglaa Zayed: Conceptualization, Formal analysis, Writing - review & editing**.** Mohamed Said: Conceptualization, Supervision. Rana Mostafa: Investigation. Aly Gaballah: Conceptualization, Supervision. Ayman Yosry: Conceptualization, Supervision.

Ethics approval: The study was conducted according to the principle of the Declaration of Helsinki, all the patients signed informed consent.

List of abbreviations:

ALT: alanine transaminase
AST: aspartate transaminase
ANA: antinuclear antibody
AFP: alfa fetoprotein
CR: clinical response
DAAs: direct-acting antiviral agents
DAC: daclatasvir
EHMs: extrahepatic manifestations
Hb: hemoglobin
HCV: Hepatitis C virus
INF: interferon
INR: international normalization ratio
LSM: liver stiffness measurements
MCV: mixed cryoglobulinemia vasculitis
MOHP: Ministry of Health and Population
NR: no response
PLT: platelets
PR: partial response
RBV: ribavirin
RF: rheumatoid factor
SIM: simeprevir
SOF: sofosbuvir
SVR: sustained virological response
TSH: thyroid-stimulating hormone**.**

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