Efficacy and safety of sofosbuvir-based, interferon-free therapy

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Efficacy and safety of sofosbuvir-based, interferon-free therapy

The Management of rheumatologic extrahepatic manifestations associated with chronic hepatitis C virus infection

Introduction

Chronic hepatitis C virus (HCV) infection is a major public health problem with 130–170 million people or 3% of the world’s population affected worldwide [1]. Chronic HCV infection is now considered to be a systemic disease which can be accompanied by extrahepatic manifestations (EHM) in up to one third of the patients. Many of these are autoimmune in nature or secondary to the chronic inflammatory process [2, 3]. The HCV is both hepatotropic and lymphotropic. This lymphotropism leads to chronic stimulation of B-cells with production of cryoglobulins, which are immune complexes that precipitate at temperatures lower than 37°C and redissolve on warming, as well as an array of organ-specific and non-organ-specific antibodies. Although cryoglobulins can be found in 40–60% of patients with chronic HCV infection only a minority of these develop systemic vasculitis related to the deposition of cryoglobulins in tissues with subsequent complement activation [4, 5]. Fatigue has been described in more than half of chronic HCV patients [6]. Joint affection is mainly in the form of polyarthralgia affecting 5% of subjects [2]. Arthritis occurs less frequently and presents as a symmetric rheumatoid-like polyarthritis in two thirds of affected subjects or less commonly as an intermittent oligoarthritis. The arthritis is generally non-erosive and may occur as a part of cryoglobulinemic vasculitis (CV) [7].

The treatment of EHM can be directed at the viral trigger and/or the downstream events in the inflammatory cascade using immunosuppressive treatment. The choice of treatment is made according to the severity of EHM and the tolerability to and effectiveness of antiviral therapy [3]. The standard anti-viral regimen until recently has been pegylated interferon alpha (Peg-IFNa)/ribavirin combination therapy with sustained viral response rates (SVR) of approximately 50%; however, the worsening of autoimmune rheumatic manifestations or their appearance de novo, has been a concern in patients with HCV vasculitis due to the immunomodulatory effects of interferon [8]. The introduction of the direct acting antiviral (DAA) drugs has revolutionized the therapy for chronic HCV with SVR achieved in 60–100% of patients. The HCV genotype 4 is the most common genotype in Egypt [9]. Sofosbuvir is a second generation DAA, approved in Europe since 2014, that can be combined with another DAA (e.g. simeprevir) or Peg-IFNa/ribavirin for treatment of HCV genotype 4 [10]. Sofosbuvir/ribavirin combination has also been used with high viral response rates for treatment of HCV genotype 4 and HCV-related cryoglobulinemic vasculitis [9, 11].

The aim of the present study was to describe the outcome of patients with HCV-related EHM using sofosbuvir-based antiviral combination therapy in comparison to a historical cohort that had previously received the standard Peg-IFN α/ribavirin regimen.

Materials and methods

A total of 24 HCV patients with rheumatologic EHM manifestations in the form of arthropathy (arthralgia/arthritis) or vasculitis who received sofosbuvir-based antiviral regimens, with no history of previous antiviral treatment (Group A) and a historical control group comprising 15 patients with arthropathy who had previously received the standard Peg-IFNa/ribavirin combination therapy (Group B) were included in this prospective retrospective study. They were recruited from the Rheumatology and Rehabilitation and Tropical Medicine departments, Faculty of Medicine, Cairo University Hospital. Sofosbuvir-based antiviral therapy is sponsored by the Egyptian Government. Informed consent to participate in the study was obtained from each patient before starting treatment. The research protocol was approved by the local Ethics Committee and conforms to the provisions of the Helsinki Declaration from 1964.

Patients were included if they had HCV viremia and HCV-related arthropathy or vasculitis and received antiviral therapy. All patients with vasculitis were classified using the classification criteria for CV, which are also useful for classify-
ing CV in patients with negative serum cryoglobulin on initial laboratory testing [12]. The exclusion criteria were: the presence of hepatitis B surface antigen, human immunodeficiency virus, patients with contraindications to antiviral therapy (e.g. pregnancy, uncontrolled thyroid disease, ischemic heart disease and advanced renal disease) and those with classical autoimmune rheumatic diseases. Patients of group A were evaluated prospectively, while the data for group B patients were collected retrospectively. Clinical data, laboratory tests and liver imaging results were available for both groups at baseline assessment (visit 0, V0), at the end of treatment (V1), 3 months after the end of treatment (V2) and 6 months after completion of drug intake (V3) to document the response to treatment and the occurrence of adverse events.

Clinical assessment of the studied patients

Articular involvement (including patients with vasculitis) was evaluated by 28 tender joint (TJC) and swollen joint counts (SJC) and a patient global pain assessment using a visual analogue scale (VAS) [13]. The degree of fatigue was assessed in all patients using the Fatigue Assessment Scale (FAS) which includes 10 questions referring to how a person usually feels. For each statement the patient can choose one out of five answer options (1 = never, 2 = sometimes, 3 = regularly, 4 = often and 5 = always). Possible scores range from 10–50 with higher scores indicating more fatigue [14].

The disease activity in patients with vasculitis was assessed using the Birmingham Vasculitis Activity Score (BVAS) 2003. This score is a clinical index of the degree of vasculitis activity in nine separate organ systems, namely the systemic, cutaneous, mucous membranes/eyes, ear, nose and throat (ENT), chest, cardiovascular, abdominal, renal and nervous systems. The maximum score for persistent abnormalities is 33, and for new/worse symptoms and signs, it is 63 [15]. A complete clinical response was defined as improvement in all baseline clinical manifestations at the end of treatment and absence of clinical relapse. A partial clinical response was defined as improvement in at least one half of the baseline clinical manifestations. Other patients were considered non-responders [16].

Laboratory investigations

Laboratory evaluation included complete blood count (CBC), erythrocyte sedimentation rate (ESR), serum rheumatoid factor (RF), detection of circulating antinuclear antibodies (ANA), liver function tests including alanine transaminase (ALT), aspartate transaminase (AST), prothrombin concentration (PC) and international normalized ratio (INR), serum creatinine, complement components 3 and 4 (C3 and C4). Cryoglobulins were isolated by centrifugation of refrigerated patient serum in Win-trobe’s tubes. Positive cryoglobulinemia was considered according to the hospital laboratory in patients who had a measurable cryocrit level >3%. Viral load was assessed by a reverse transcriptase polymerase chain reaction (RT-PCR) assay (Applied Biosystems, QIAamp® DSP Virus Spin Kit [QIAGEN, Germany]) with a lower limit detection level of 10 IU/ml at baseline assessment (V0). Qualitative PCR was performed on week 4 after the start of treatment, at the end of treatment (V1), 12 weeks (V2) and 24 weeks (V3) after completion of treatment. The following definitions were used to define virological response: a rapid virological (RVR) response is HCV RNA negative at treatment week 4; end of treatment negative response (ETR), is HCV RNA negative at the end of treatment week 4; sustained virological response SVR12 and SVR24, are HCV RNA negative at 12 weeks and 24 weeks after cessation of treatment, respectively. All patients who do not achieve a SVR24 are classified as virological non-responders [17, 18].

Liver imaging

Evaluation of the liver condition included abdominal ultrasonography and transient elastography (FibroScan® device [Echosens, Paris]), that is correlated with the Metavir scoring system for liver fibrosis [19].

Treatment

Patients (group A) received one of the following sofosbuvir-based combination regimens based on liver disease severity and tolerance to ribavirin: daily sofosbuvir (400 mg) and simeprevir (150 mg) for 12 weeks or daily sofosbuvir (400 mg) and daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) for 24 weeks. For prudence, in patients with severe manifestations of vasculitis immunosuppressive treatment was started before the initiation of antiviral therapy. All patients receiving antirheumatic drugs were allowed to continue their treatment during the study. The historical control group (group B) comprised 15 patients with HCV-related arthropathy who had previously received the standard combined weekly Peg-IFNa and daily weight-based ribavirin for 48 weeks in responders, while those who showed no response discontinued the treatment earlier.

Methods of statistical analysis

The prospective data of the patients and the retrospective data of historical controls were analyzed using the statistical program SPSS version 15. Results were expressed as mean ± standard deviation (SD), or number and percentage. Student’s t-test was used to compare continuous variables between HCV patients and controls, and between subgroups of HCV patients. The Kruskal-Wallis test was used for comparing two independent samples of different sample sizes. The χ²-test for the categorical variables was performed when appropriate. The Friedman test is the non-parametric alternative to the one-way ANOVA that is used for the repeated measures in the follow-up visits within the same group of patients. The level of statistical significance was <0.05 (2-tailed).

Results

The baseline characteristics of both groups are shown in Table 1 and 2.
Efficacy and safety of sofosbuvir-based, interferon-free therapy. The Management of rheumatologic extrahepatic manifestations associated with chronic hepatitis C virus infection

Abstract
Background. The use of pegylated interferon alpha (IFN) has been of concern in chronic hepatitis C virus (HCV) patients with rheumatologic extrahepatic manifestations (EHM) due to the immunostimulatory effects of IFN.

Aim. To study the efficacy and safety of sofosbuvir-based, IFN-free antiviral therapy in chronic HCV patients with rheumatologic EHM.

Material and methods. Group A included 24 patients with arthropathy (arthralgia or arthritis, n = 15) or vasculitis (n = 9) who received sofosbuvir and ribavirin (n = 17) or sofosbuvir and simeprevir (n = 7). Group B comprised 15 historical controls suffering from arthropathy who had received IFN and ribavirin. All patients were clinically evaluated and by detection of HCV viremia at baseline (V0), at the end of treatment (V1), 12 weeks after end of treatment (V2) and 24 weeks after end of treatment (V3).

Results. Sustained viral response was obtained in all patients of group A (100%) versus 12 out of 15 of group B (80%). In group A, the tender joint count (TJC) and visual analogue scale for pain (VAS) improved (p = 0.001 for both) while the swollen joint count (SJC) decreased at V1 (p = 0.001) but returned to baseline values at V3. All vasculitis patients improved. Purpura, arthralgia and leg ulcers disappeared, but peripheral neuropathy persisted. In group B, TJC, SJC and VAS increased from baseline values (p = 0.034, 0.03 and 0.001, respectively). Side effects in group A were generally mild, but one patient developed deterioration of arthralgia.

Conclusion. The use of IFN-free regimens is safe and effective in the treatment of most HCV-related rheumatologic EHM.

Keywords
Hepatitis C virus · Extrahepatic manifestations · Arthritis · Vasculitis · Sofosbuvir

The mean age of group A patients was significantly higher than that of group B (p = 0.02) while the male: female ratio was not significantly different between both groups. Laboratory parameters and viral load were not significantly different between both groups while the fibroscan results showed that a higher proportion of group A patients had mild forms of liver fibrosis (F0–F2) as compared to group B (p = 0.03).

Among group A, 15 patients had arthropathy and 9 patients had vasculitis. The manifestations of vasculitis included fatigue in 7 patients, arthralgia in 6 and arthritis in 3 patients, cutaneous involvement in the form of purpura in 9 patients, ulcers and toe gangrene in 1 patient, neurological involvement in the form of mononeuritis multiplex in 1 patient and sensory peripheral neuropathy in 3 patients. One patient suffered from central nervous system involvement in the form of severe headache and cognitive affection manifested by memory loss and lack of concentration. Only 2 patients had detectable cryoglobulins and low C3 and C4. The mean (BVAS) at baseline was 3.8 ± 1.8. Group A patients received sofosbuvir in combination with ribavirin (n = 17) or with simeprevir (n = 7) and two patients with vasculitis received 6-monthly pulsed cyclophosphamide.
before the initiation of antiviral therapy. During the time of the study, 14/24 (58.3%) of group A (including 5 patients with arthritis and 9 with vasculitis) were on prednisolone (5–30 mg/day), 4 (16.7%) patients with arthritis received methotrexate, 2 others (8.3%) received leflunomide and 1 patient (4.2%) with vasculitis received azathioprine. Among group B, 4/15 (26.7%) patients were on 5–10 mg/day prednisolone, 3 (20%) received methotrexate and 2 (13.3%) received leflunomide.

### Virological response

All patients of group A (100%) showed a RVR, ETR, SVR12, and SVR24 while among group B, 12/15 (80%) patients showed ETR, SVR12 and SVR24.

### Clinical response

At V0, the FAS, TJC, SJC and VAS were significantly lower in group A at V2 and V3 (p = 0.002 and 0.01, respectively). Comparing the individual follow-up visits between groups A and B revealed no statistically significant differences in the FAS at V1, V2 and V3 while the TJC and VAS were significantly lower in group A (p = 0.001 at V1, V2 and V3). The SJC was not significantly different between both groups at V1 but was significantly lower in group A at V2 and V3 (p = 0.002 and 0.01, respectively). Fig. 1

The statistical analysis was repeated for group B patients after removal of the three patients who had no virological response (group B*) to show the changes of FAS, TJC, SJC and VAS in virological responders only. The changes of FAS scores from V0 (9.08 ± 13.46) to V3 (10.58 ± 15.73) were not statistically significant (p = 0.25). The changes in TJC were also non-significant between V0 (6.5 ± 7.74) and V3 (7.6 ± 8.55, p = 0.09). On the other hand, the SJC increased significantly from V0 (1.5 ± 1.45) to V3 (5.2 ± 6.98, p < 0.001) and the VAS also increased significantly from V0 (60 ± 12.79) to V3 (75 ± 13.82, p = 0.001). Comparing group A and group B* at V0 showed that FAS, TJC, SJC and VAS were not significantly different. There were also no statistically significant differences between both groups at the FAS at V1, V2 and V3 while the TJC and VAS were significantly lower in group A at V1, V2 and V3 (p = 0.001). The SJC was not significantly different between both groups at the FAS at V1, V2 and V3 while the TJC and VAS were significantly lower in group A at V1, V2 and V3 (p = 0.001).
Assessment of fatigue and articular symptoms in chronic HCV patients in response to antiviral therapy: Gr. A group A treated by sofosbuvir-based anti-viral regimens; Gr. B group B treated by pegylated interferon/ribavirin (historical control group). V0 visit at baseline assessment; V1 visit 1 at end of treatment, V2 visit 2 at 12 weeks after end of treatment, V3 visit 3 at 24 weeks after end of treatment; FAS fatigue assessment scale, TJC tender joint count, SJC swollen joint count, VAS visual analogue scale for pain. Mean values are presented by V1, but significantly lower in group A at V2 and V3 (p = 0.003 and 0.02, respectively). Fig. 2.

All patients with vasculitis included in the study responded to treatment with steroids, cytotoxic drugs and antiviral therapy. The BVAS results of the nine patients showed a significant improvement (3.8 ± 1.8 at V0, 1.35 ± 0.5 at V1, 1.52 ± 0.58 at V2 and 1.53 ± 0.5 at V3, p = 0.04). By the end of treatment (V1) among patients with vasculitis 5 (56%) patients were complete clinical responders and 4 (44%) were partial clinical responders. Purpura and articular manifestations disappeared. Skin ulcers were present in 1 patient and improved by week 4 and completely healed by the end of treatment. The central nervous system manifestations in one patient improved completely at the end of treatment with sofosbuvir and ribavirin, while the peripheral neurological manifestations persisted in all 4 patients.

Biochemical and immunological response

All patients with elevated ALT and AST in groups A and B showed normalization of the levels of ALT and AST starting from V1 and remained normal at V2 and V3. Most patients of groups A and B showed no change in immunological data (RF, ANA, C3, C4 and cryoglobulins). Only one patient in group A suffering from vasculitis developed low C4, and among group B, one patient became RF +ve and another patient showed low C4 at V2.

Side effects of antiviral therapy

The side effects of antiviral therapy in all patients are summarized in Table 3. None of these side effects necessitated treatment discontinuation. One patient who was on sofosbuvir and ribavirin developed a skin rash on the dorsum of the hand during treatment that disappeared by V2. Sensory neuropathy appeared de novo in one patient from group B. The proportion of patients who developed treatment-related side effects was significantly higher in group B (p = 0.02). Worsening of arthralgia was reported more frequently among group B patients (p = 0.02) while other side effects were not significantly different between both groups.

Discussion

The DAA have revolutionized therapy for HCV and have raised the hope towards eradication of HCV infection due to the increased SVR rates and improved safety profile [9]. The effect of the DAAs on HCV-related EHM has only been reported in a few studies [11, 20, 21]. In the present study, we were able to demonstrate the superiority of sofosbuvir-containing regimens over the traditional Peg-IFNα/ribavirin antiviral therapy in terms of achievement of SVR and improvement...
Assessment of fatigue and articular symptoms in chronic HCV patients who had a sustained virological response after antiviral therapy; Gr. A group A treated by sofosbuvir-based anti-viral regimens; Gr. B virological responders from group B treated by pegylated interferon/ribavirin (historical control group). V0 visit at baseline assessment, V1 visit 1 at end of treatment, V2 visit 2 at 12 weeks after end of treatment; V3 visit 3 at 24 weeks after end of treatment; FAS fatigue assessment scale, TJC tender joint count, SJC swollen joint count, VAS visual analogue scale for pain. Mean values are presented.

Patients in the present study were classified according to the antiviral treatment they received into group A (including patients with arthropathy and vasculitis who received sofosbuvir-containing antiviral regimens) and group B (including patients with arthropathy who had previously received the standard Peg-IFN α/ribavirin therapy). Among both patient groups, those receiving corticosteroids with or without immunosuppressive drugs, were allowed to continue their anti-rheumatic treatment.

On virological assessment; SVR12 and SVR24 were seen in 100% and 80% of patient groups A and B, respectively. Other studies using the standard Peg-IFNα/ribavirin regimen in HCV patients with rheumatologic EHM including vasculitis and arthropathy, reported SVR 24 ranging from 10–67.5% [20, 22–24]. Studies with available viral genotyping included mixed viral genotypes, predominantly genotype 1 [22, 23]. In CV patients (mixed viral genotypes, predominantly genotype 1) treated by sofosbuvir-based DAA regimens, the SVR 12 ranged from 74–100% [11, 20, 21].

On follow-up of our patients in group A, although the number of patients complaining from fatigue did not change, significant improvement was detected on comparing FAS throughout the follow-up visits. In group B, however, there was no significant change in the number of patients suffering from fatigue or FAS. The FAS did not change also when only virological responders from group B were considered. In agreement with our results from group B, Dirks et al. [25] found that the fatigue impact scale in addition to other neuropsychiatric tests were not statistically significantly different among four HCV patient groups, who were either PCR +ve (who failed Peg-IFNα/ribavirin therapy or were not treated) or PCR-ve (who cleared the virus spontaneously or after Peg-IFNα/ribavirin therapy), while being significantly higher than in the control group. The authors suggested that the persistent cerebral dysfunction after viral clearance may be explained by an autoimmune process triggered by HCV infection, that may persist after viral eradication or alternatively, as there is evidence for the ability of HCV to invade and replicate in the brain [26], by the persistence of a virus variant in the brain despite the eradication of the virus from the peripheral circulation. On the
In agreement with our results, other investigators reported occurrence of Peg-IFNα-related side effects in 48.1% and 100% of patients with HCV-related arthropathy and vasculitis, respectively [20, 24]. Worsening of arthralgia occurred more frequently among group B and severe sensory peripheral neuropathy developed de novo in one patient. Other investigators [24, 30] also reported that the most frequent rheumatologic manifestations attributable to Peg-IFNα therapy in HCV patients were the development of peripheral neuropathy and articular involvement. Therefore, in patients with rheumatologic EHM, interferon-free antiviral regimens seem to be a safer choice. Concerning side effects related to sofosbuvir-based DAA therapy in vasculitis patients, the frequency ranged from 58%–67%, [11, 20, 21], higher than in our study. Side effects were generally mild but serious adverse events leading to treatment interruption or emergency department evaluation occurred in 8%–17% of patients in the form of hallucinations and irritability, anxiety and insomnia, severe anemia and hyperkalemia [11, 20]. Of note, in the present study, 1/17 patients receiving sofosbuvir and ribavirin experienced worsening of arthralgia. The significance of this adverse event needs to be explored in a further study including more patients.

To conclude, sofosbuvir containing interferon-free antiviral regimens were effective in achieving viral eradication in 100% of patients with clinical improvement of most EHM and good tolerability, however, a longer period of follow-up is needed to confirm these results. Peg-IFNα may worsen or trigger new EHM and should be avoided in HCV patients with rheumatologic EHM.

### Table 3 Side effects of effects in interferon-free (group A) and interferon- treated patients (group B)

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Group A (n = 24)</th>
<th>Group B (n = 15)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening of arthralgia</td>
<td>1 (4%)</td>
<td>5 (33%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Worsening of arthritis</td>
<td>0</td>
<td>2 (13%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>0</td>
<td>1 (7%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Skin rash</td>
<td>1 (4%)</td>
<td>0</td>
<td>0.4</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (13%)</td>
<td>0</td>
<td>0.27</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1 (4%)</td>
<td>0</td>
<td>0.42</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (8%)</td>
<td>2 (13%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>0</td>
<td>2 (13%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>2 (13%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Patients with side effects</td>
<td>6 (25%)</td>
<td>10 (66.7%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

other hand, a previous study reported that fatigue increased during Peg-IFNα/ribavirin therapy of chronic HCV but started to decrease after termination of therapy and reached lower levels than baseline by 12 weeks after discontinuation of treatment [27]. Contrary to our results, in another study the frequency of HCV patients with EHM complaining of fatigue decreased from 92.6% to 37% after Peg-IFNα/ribavirin therapy [24]. The impact of sofosbuvir/ribavirin therapy in chronic HCV infection on patient reported outcomes (PRO); including fatigue was described in the VALENCE study. Modest declines of PRO were observed which returned to baseline levels 12 weeks after treatment. Patients who achieved SVR12 had significant improvement in fatigue and other PROs [28].

Regarding articular manifestations, TJC and VAS improved significantly in group A, while the SJC decreased initially and returned to baseline values 24 weeks after completion of treatment. On the other hand, the TJC, SJC and VAS worsened significantly in group B while in virological responders from group B, the TJC did not change and the SJC and VAS worsened significantly. Concerning the effect of standard Peg-IFNα/ribavirin on HCV patients, in agreement with our results from group B, a previous study reported that among 23 patients with arthropathy, only 39% improved while 61% did not respond or became worse [24]. In another study, the number of tender joints and VAS for pain did not decrease significantly with treatment [29]. Probably, in predisposed subjects, alpha-interferon which is both an antiviral and immunomodulating agent can trigger or exacerbate some pre-existing symptoms [8]. There is paucity of data regarding the effect of sofosbuvir-containing regimens on HCV-related articular manifestations. Saadoun et al. [11] reported that the arthralgia affecting 14/24 (58%) of mixed CV patients disappeared by the end of treatment with sofosbuvir/ribavirin for 24 weeks. Among group A, patients with vasculitis improved on treatment by steroids with or without cytotoxic drugs and antiviral therapy as monitored by the BVAS with 56% achieving a complete clinical response and 44% a partial response. Purpura, arthralgia, skin ulcers and cognitive abnormalities disappeared by the end of treatment while peripheral neuropathy persisted. Saadoun et al. [11] found that by the end of treatment with sofosbuvir/ribavirin, 87.5% of CV patients were complete clinical responders and 12.5% were partial responders. Purpura, skin ulcers and arthralgia disappeared in all cases while renal and neurological manifestations persisted in some patients. Gragnani et al. [21] reported that by SVR24 all patients with vasculitis showed a clinical response; 77% showed disappearance or improvement of all manifestations and 23% had a partial response with peripheral neuropathy and sicca manifestations tending to persist.

In the present study, 6 (25%) of group A patients developed mild side effects compared to 10 (66.7%) of group B. In agreement with our results, other investigators reported occurrence of Peg-IFNα-related side effects in 48.1% and 100% of patients with HCV-related arthropathy and vasculitis, respectively [20, 24]. Worsening of arthralgia occurred more frequently among group B and severe sensory peripheral neuropathy developed de novo in one patient. Other investigators [24, 30] also reported that the most frequent rheumatologic manifestations attributable to Peg-IFNα therapy in HCV patients were the development of peripheral neuropathy and articular involvement. Therefore, in patients with rheumatologic EHM, interferon-free antiviral regimens seem to be a safer choice. Concerning side effects related to sofosbuvir-based DAA therapy in vasculitis patients, the frequency ranged from 58%–67%, [11, 20, 21], higher than in our study. Side effects were generally mild but serious adverse events leading to treatment interruption or emergency department evaluation occurred in 8%–17% of patients in the form of hallucinations and irritability, anxiety and insomnia, severe anemia and hyperkalemia [11, 20]. Of note, in the present study, 1/17 patients receiving sofosbuvir and ribavirin experienced worsening of arthralgia. The significance of this adverse event needs to be explored in a further study including more patients.

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Compliance with ethical guidelines

Conflict of interests. A.A. Shahin, H.S. Zayed, M. Said and S.A. Amer declare that they have no competing interests.

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