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Three regimens for re-treatment failure of Sofosbuvir-based therapy for chronic hepatitis-C genotype-4: a cohort study

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ABSTRACT

Despite the high sustained virologic response (SVR) rates of direct-acting antiviral (DAAs) therapy, a small number of patients does not eradicate the virus, and these patients represent a challenge. This study aims to compare the outcomes of three second-line regimens for DAAs-experienced patients with chronic hepatitis C (CHC). This prospective observational study was conducted at the Damanhur Viral Hepatitis Center from January 2017 to February 2020. We included patients with CHC who did not achieve SVR after the complete course of Sofosbuvir/Daclatasvir±Ribavirin (SOF/DAC±RBV). The primary endpoint was SVR-12 after re-treatment. This study included 360 patients (with a mean age of 51.53±11.38 years). Approximately 51.1% of the patients were males, and 65.5% had liver cirrhosis. All patients of group 1 (45 patients) received SOF/VEL/VOX over 12-weeks; SVR-12 was achieved in 44 patients (97.8%). Group 2 (28 patients) received SOF/DAC/RBV over 24-weeks; (one patient was lost during follow-ups and one patient discontinued treatment due to hepatic decompensation). SVR-12 was achieved in 25 patients (96.2%). Group 3 (287 patients) received SOF/Ombitasvir/Paritaprevir/Ritonavir/RBV) over 12-weeks. Eight patients were lost during follow-ups, and one patient discontinued treatment due to grade 4 adverse events. SVR-12 was achieved in 276 patients (99.3%). There was no difference between the groups regarding their age, gender distribution, baseline viral load or comorbidities. Adverse events (thrombocytopenia, anemia, hyperbilirubinaemia and prolonged INR) were significantly higher in group 3, while group 1 did not experience any. The three studied retreatment regimens can be used for DAAs treatment-experienced patients considering availability. The SOF/VEL/VOX combination had the least adverse events.

KEYWORDS: Direct-acting antivirals. Hepatitis C virus. Velpatasvir. Voxilaprevir. Daclatasvir. Ribavirin. Ombitasvir/Paritaprevir/Ritonavir. Treatment-experienced.

INTRODUCTION

Chronic hepatitis C infection (CHC) is one of the major causes of chronic liver disease, liver cirrhosis and hepatocellular carcinoma worldwide. In 2015, the World Health Organization (WHO) announced that serologic evidence of hepatitis C virus (HCV) was detected in approximately 100 million people in the world and 71 million were infected with CHC (prevalence of 1%)[1]. As reported in 2008, Egypt had the highest HCV burden globally[2] with genotype 4 affecting more than 94% of patients[3,4]. In 2015, the seroprevalence of HCV infection had declined to 6.3%[5] with an estimated overall prevalence reduction of 30%, particularly after the introduction of direct-acting antiviral therapy (DAAs)[6]. By 2018, more than two million people with CHC received DAAs (40% of the infected population), with SVR rates over 90%[7].

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Despite the high sustained virologic response (SVR) rates of DAAs, a small number of patients does not eradicate the virus, and these patients represent a challenge[8]. The Sofosbuvir (SOF)/Velpatasvir (VEL) and a second-generation HCV-protease inhibitor, Voxilaprevir (VOX), is a pan-genotypic DAAs combination and the only combination approved for treatment-experienced patients, including those who received non-structural-5A inhibitors. Real-world experiences are still needed for this combination[8]. Unfortunately, current salvage therapies are not accessible in many regions and there are limited data available about the efficacy of different retreatment regimens[9].

In the absence of approved regimens for DAAs treatment-experienced patients, WHO reported that expert consultation advised that extending the primary DAA regimen to 16 or 24 weeks, in addition to boosting treatment adherence, could be an alternative for retreatment[10].

The phase 2b PEARL-I study reported that the 12-week DAAs combination of once-daily Ombitasvir (OMB), Paritaprevir (PAR) and the pharmacoenhancer Ritonavir (RIT) plus twice-daily Ribavirin (RBV), achieved SVR in all treated patients with HCV genotype 4 without cirrhosis (treatment-naive [n = 42] and treatment-experienced [n = 49])[11]. The phase 3 AGATE-I trial results showed that the same combination also had high efficacy and safety in patients with genotype-4 and compensated liver cirrhosis when treated for 12 or 16 weeks (SVR-12 rates of 97% and 100%, respectively), while treatment prolongation to 24 weeks did not show additional benefits[12].

There is a scarcity of data on the retreatment of patients with genotype 4 who have failed prior DAAs therapy. The principal factors that influence the choice of the retreatment regimen are (1) the type of prior regimen, (2) liver cirrhosis, and (3) cost or insurance concerns. Resistance-associated substitutions (RAS) testing is not routinely recommended for treatment-experienced patients with genotype 4. The AASLD-IDSA guidelines recommend a daily fixed-dose combination of SOF (400 mg)/VEL (100 mg)/VOX (100 mg) and the addition of RBV for patients with cirrhosis[13]. Sixteen weeks of Glecaprevir/Pibrentasvir is an alternative regimen[13].

This study aimed to compare the outcomes of three regimens of second-line treatment for DAAs-experienced patients (SOF, VEL and VOX combination, versus SOF, Daclatasvir (DAC), and RBV combination versus SOF, OMB, PAR, and RIT combination with or without RBV).

MATERIALS AND METHODS

This prospective observational cohort study was conducted at the Damanhur Viral Hepatitis Center (Beheira Governorate), affiliated with the Egyptian National Committee for Control of Viral Hepatitis (NCCVH), from January 2017 to February 2020. We included adult male and female patients (older than 18 years) with chronic hepatitis C, with and without liver cirrhosis, who had previously been treated with the complete course of the combination of SOF/DAC, with and without RBV, who then did not achieve SVR (undetectable HCV viral load after 12 weeks of the end of treatment). We included all patients who attended the center within the duration of the study.

We excluded patients with renal impairment, patients co-infected with HBV or HIV, patients with hepatocellular carcinoma and patients with decompensated liver cirrhosis.

The study was performed in compliance with the ethical principles of the 1975 Declaration of Helsinki and its later amendments (as revised in Brazil in 2013) with good clinical practice (GCP) guidelines. The study was approved by the ethical committee of the Faculty of Medicine, Cairo University. All patients signed an informed consent form. The study was reported according to the STROBE guidelines.

Patients were assigned to receive a second-line treatment regimen for 12 or 24 weeks according to the protocol of the national committee for control of viral hepatitis[14] and according to the available medication at the time of enrollment. Patients were classified into three groups according to the second line of treatment. Group 1: patients who received SOF 400 mg, VEL 100 mg, and VOX 100 mg (SOF/VEL/VOX) combination, one tablet, orally, once daily for 12 weeks (45 patients, 12.5%), of whom three patients received SOF/VEL/VOX and RBV; Group 2: patients who received SOF 400 mg, DAC 60mg, and RBV for 24 weeks (28 patients, 7.8%), we used this combination due to lack of availability of other regimens at the time of recruitment; Group 3: patients who received SOF 400 mg, and OMB 12.5 mg, PAR75 mg, RIT 50 mg combination and RBV (SOF/OMB/PAR/RIT/RBV) for 12 weeks (287 patients, 79.7%).

The RBV recommended dose was 1200 mg daily if the patient's weight was above 75 kg, and 1000 mg daily if the patient's weight was less than 75 kg, given in two doses. RBV was added to our treatment-experienced patients if one of the criteria for the difficulty-to-treat (according to the guidelines of the NCCVH) was present; total bilirubin > 1.2, Serum albumin < 3.5, INR > 1.2 or Platelets < 150000, or if they had liver cirrhosis (as determined by clinical and ultrasonographic examination) and/or varicose veins, F3-F4 stages on Metavir score with Fib-4 > 3.25[15].

Baseline demographic, clinical, laboratorial and abdominal ultrasound characteristics were collected. A non-invasive assessment of the fibrosis stage was done using the Fibrosis-4 score (FIB-4) and Transient Elastography (FibroScan), and cirrhosis was defined as a liver stiffness measurement of greater than 14 kPa. The

FIB-4 score was calculated for all patients using Sterling's formula = [age (years) x AST (IU/L)]/[platelet count (109/L) x ALT (IU/L) 1/2][16].

The primary endpoint of this study was SVR at 12-weeks after the end of the second-line treatment regimen (SVR12).

Follow up

In this study, patients were subjected to a monthly follow-up during the second-line treatment period and at 12 weeks after the end of treatment to confirm SVR. Follow-up was performed clinically with the usage of routine laboratory data, ultrasonography and quantitative HCV-PCR to detect SVR12.

Statistical analysis

The data were coded and entered using the Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). For quantitative data, we used mean, standard deviation, median, minimum, and maximum, while frequency (count) and relative frequency (percentage) were used for categorical data. The comparisons between quantitative variables were made using the non-parametric Kruskal-Wallis's and Mann-Whitney's tests[17]. For comparing categorical data, the Chi-square (χ^2) test was performed. An exact test was used instead when the expected frequency was less than 5[18]. P-values less than 0.05 were considered statistically significant. For comparison of serial measurements within each patient the non-parametric Friedman's test and Wilcoxon's signed rank test were used.

RESULTS

This study included 360 patients who did not achieve SVR after a complete course of SOF/DAC (184 patients, 51.1%) or SOF/DAC/RBV (176 patients, 48.9%) for their CHC. The mean age of the included patients was 51.53 ± 11.38 years old. Patients were predominantly males (184 patients, 51.1%), and liver cirrhosis was present in 236 patients (65.5%). There was no significant difference between the three groups regarding their age, gender distribution or comorbidities (Table 1). Patients with liver cirrhosis were significantly higher in groups 2 and 3,

Table 1 - Demographics and treatment outcome of the 3 studied groups.

		SOF/VEL/VOX± RBV 45 (12.5%) patients		SOF/DAC/RBV 28 (7.8%) patients		SOF/OMB/PAR/RIT/RBV 287 (79.7%) patients		P value
		Count	Percent	Count	Percent	Count	Percent	
Age in years (mean and SD)		52.33	14.07	48.25	13.43	51.72	10.67	0.325
Gender	Male	20	44.4%	17	60.7%	147	51.2%	0.399
	female	25	55.6%	11	39.3%	140	48.8%	
First treatment regimen	SOF/DAC	33	73.3%	14	50.0%	137	47.7%	**0.006**
	SOF/DAC/RBV	12	26.7%	14	50.0%	150	52.3%	
Hypertension		2	4.4%	1	3.6%	32	11.1%	0.263
Diabetes Mellitus		8	17.8%	4	14.3%	48	16.7%	0.932
Liver	Cirrhotic	21	46.7%	20	71.4%	195	67.9%	**0.007**
	Non-cirrhotic	24	53.3%	8	28.6%	92	32.1%	
Side effects during the second treatment regimen	Prolonged INR	0	0.0%	1	3.6%	10	3.4%	**0.01**
	elevated bilirubin	0	0.0%	3	10.8%	51	17.7%	
	Anemia	0	0.0%	1	3.6%	22	7.6%	
	thrombocytopenia	0	0.0%	1	3.6%	3	1.0%	
	Decompensation with marked ascites	0	0.0%	1	3.6%	0	0.0%	
HCV RNA 24	positive (non-responders)	1	2.2%	1	3.8%	2	0.7%	0.183
	negative (responders) within patients who completed treatment regimen	44	97.8%	25	96.2%	276	99.3%	
	negative (responders) within total	44/45	97.78%	25/28	89.28%	276/287	96.16%	0.143

SOF = Sofosbuvir; VEL = Velpatasvir; VOX = Voxilaprevir; OMB = Ombitasvir; PAR = Paritaprevir; RIT = Ritonavir; RBV = Ribavirin; DAC = Daclatasvir; SD = standard deviation; HCV = hepatitis C virus. Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency was less than 5.

Table 2 - Comparison between baseline characteristics of the 3 studied groups.

	SOF/VEL/VOX± RBV 45 (12.5%) patients		SOF/DAC/RBV 28 (7.8%) patients		SOF/OMB/PAR/RIT/RBV 287 (79.7%) patients		P value
	Mean	SD	Mean	SD	Mean	SD	
Log_{10} HCV RNA by PCR	5.35	0.96	5.04	1.27	5.18	1.11	0.632
ALT (IU/L)	44.60	36.35	63.85	56.07	50.89	33.77	0.166
AST (IU/L)	49.00	44.79	71.46	60.16	54.84	38.72	0.085
FIB4	2.72	2.18	4.92	4.05	3.29	2.66	0.062
AFP (IU/L)	8.04	12.89	16.49	28.63	9.92	12.12	0.142
WBCx10^3/mm^3	6.02	2.18	5.44	2.18	5.58	2.15	0.338
Plateletsx10^3/mm^3	185.76	78.30	140.93	85.64	157.32	72.78	**0.008**
Total BILIRUBIN	0.80	0.31	1.37	0.73	0.91	0.34	**0.002**
Albumin (g/dL)	4.12	0.49	3.72	0.67	3.86	0.54	**0.003**

FIB-4 = Fibrosis-4; WBC = White Blood Cell count; INR = International normalized ratio; AFP = alpha fetoprotein; ALT = Alanine Transaminase; AST = Aspartate Transaminase. Non-parametric Kruskal-Wallis's test was used.

affecting their laboratory characteristics (Table 2). There was no significant difference between the three groups regarding their HCV quantitative PCR before starting the second-line treatment.

All patients of group 1 who received the SOF/VEL/VOX±RBV combination did not experience any adverse events and completed their 12-week treatment regimen. SVR-12 was achieved in 44 (97.8%) patients and only one patient did not achieve SVR-12. Within group 2, patients received SOF/DAC/RBV for 24 weeks, one patient was lost during follow-ups and one patient discontinued treatment due to the development of hepatic decompensation and ascites, requiring hospitalization. Among the 26 patients who completed their treatment, SVR-12 was achieved in 25 (96.2%) patients and one patient (3.8%) failed to achieve SVR-12. Grade 1-2 adverse events occurred in the form of thrombocytopenia, anemia, hyperbilirubinaemia and prolonged INR. Regarding patients in group 3 who received SOF/OMB/PAR/RIT/RBV, eight patients were lost during follow-ups and one patient discontinued treatment due to grade 4 adverse events. The adverse events were significantly higher in this group (Table 2). Within the 278 patients who completed their treatment, 2 (0.7%) patients failed to achieve SVR-12 and 276 (99.3%) patients achieved SVR-12 (Table 1). The ALT, AST and platelet count significantly improved after treatment among the three treatment groups (Table 3). A flow chart of the studied patients is shown in Figure 1.

DISCUSSION

This prospective observational cohort study compared the outcomes of three retreatment regimens for DAAs treatment-experienced patients with CHC, with and without cirrhosis. The patients received different treatment regimens according to the chronological changes of the drugs available in the treatment centers of the NCCVH affiliated to the Egyptian Ministry of Health and the Population. The treatment-experienced patients were managed by separate clinics within the NCCVH centers with specialized consultants[6]. Within this study, patients who received the SOF/VEL/VOX combination, with and without RBV, showed the least adverse event profile and better SVR-12 rates. The SOF/OMB/PAR/RIT/RBV combination showed the highest rate of adverse events among the three studied regimens. Among patients who completed their 12-week treatment course, there was no difference in SVR-12 rates among the three groups.

The choice of a treatment regimen for treatment-experienced patients is a challenge. The choice of treatment for such difficult-to-treat groups should be guided by resistance-associated substitutions (RAS) analysis and the experience of the treating physicians. If RAS analysis is not available, retreatment should be guided by the knowledge of the previously-administered drugs[19]. To improve the SVR of retreatment, the used drug regimen should have several viral targets and modes of action in addition to a non-overlapping resistance analysis[19].

HCV DAAs combination regimens issued by the Egyptian National Committee for Control of Viral Hepatitis (NCCVH) for retreatment of non-responders was selected to provide the highest efficacy considering the use of drugs with a different mechanism and higher barrier of resistance than the previously-used combinations for the same patient[9]. Previously, the available retreatment options were limited to prolongation of treatment duration, the addition of RBV or novel combinations of approved DAAs (if available) until

Table 3 - Comparison between biochemical data before, during, and after treatment.

	SOF/VEL/VOX± RBV 45 (12.5%) patients		SOF/DAC/RBV 28 (7.8%) patients		SOF/OMB/PAR/RIT/RBV 287 (79.7%) patients	
	Mean	P value	Mean	P value	Mean	P value
ALT (IU/L) baseline	44.60 (36.35)	---	63.85 (56.07)	---	50.89 (33.77)	---
ALT (IU/L) (WK4)	23.80 (8.94)	< 0.001	30.91 (13.72)	0.011	28.95 (15.55)	< 0.001
ALT (IU/L) (WK8)	22.62 (7.26)	< 0.001	24.76 (10.93)	0.017	27.34 (11.31)	< 0.001
ALT (IU/L) (WK12)	22.21(9.27)	< 0.001	27.36 (10.68)	0.008	26.63 (10.90)	< 0.001
AST (IU/L) baseline	49.00 (44.79)	---	71.46 (60.16)	---	54.84 (38.72)	---
AST (IU/L) (WK4)	25.49 (7.29)	< 0.001	29.19 (14.11)	0.001	31.76 (14.20)	< 0.001
AST (IU/L) (WK8)	26.82 (7.09)	< 0.001	29.38 (12.76)	0.001	30.19 (11.36)	< 0.001
AST (IU/L) (WK12)	24.47 (6.41)	< 0.001	35.45 (14.10)	0.006	31.15 (13.15)	< 0.001
WBCx10^3/mm^3 baseline	6.02 (2.18)	---	5.44 (2.18)	---	5.58 (2.15)	---
WBC×10 (WK4)	6.17 (2.38)	0.108	5.44 (1.81)	0.615	5.84 (2.07)	0.007
WBC×10 (WK8)	6.40 (2.38)	0.154	6.03 (2.50)	0.246	5.51 (2.08)	0.615
WBC×10 (WK12)	5.97 (1.71)	0.471	5.62 (1.64)	0.609	5.47 (2.32)	0.528
Plateletsx10^3/mm^3 baseline	185.76 (78.30)	---	140.93 (85.64)	---	157.32 (72.78)	---
Platelets (WK4)	196.81 (82.86)	0.020	158.68 (88.14)	0.005	164.65 (69.21)	< 0.001
Platelets (WK8)	183.61 (72.11)	0.495	177.33 (97.39)	0.015	160.71 (72.19)	0.003
Platelets (WK12)	198.35 (88.43)	0.122	136.53 (77.59)	0.233	156.91 (74.79)	0.008
Total BILIRUBIN baseline	0.80 (0.31)	---	1.37 (0.73)	---	0.91 (0.34)	---
Total bilirubin (WK4)	0.89 (0.35)	0.117	1.68 (1.15)	0.030	1.27 (0.74)	< 0.001
Total bilirubin (WK8)	0.88 (0.34)	0.205	1.45 (0.98)	0.138	1.13 (0.59)	< 0.001
Total bilirubin (WK12)	0.88 (0.30)	0.241	1.50 (0.89)	0.814	1.21 (0.65)	< 0.001

P value compared to baseline in each group. Non-parametric Wilcoxon's signed rank test was used.

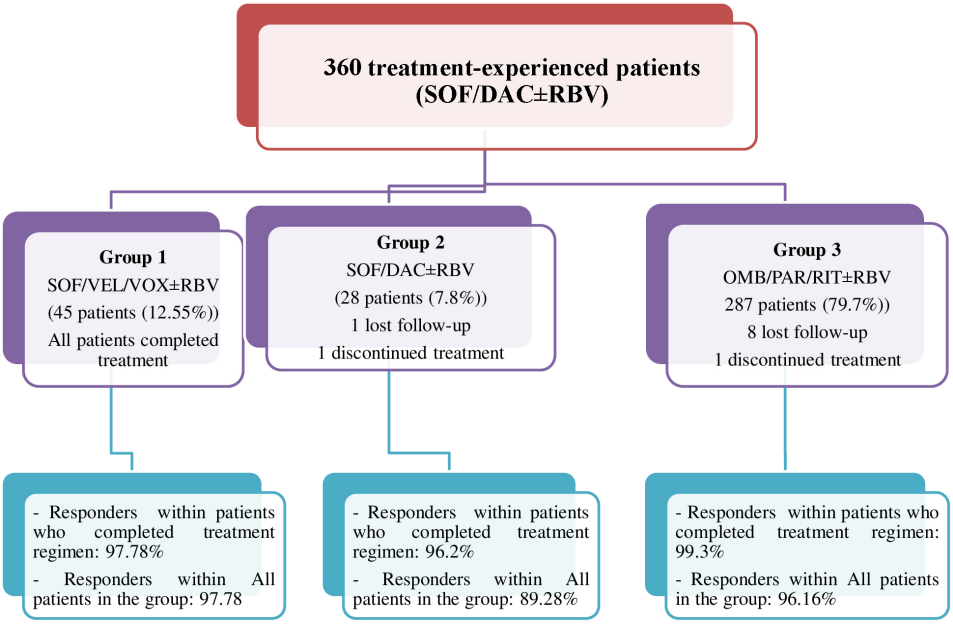

Figure 1 - Flow chart of the studied patients.

the SOF/VEL/VOX combination was approved by the Food and Drug Administration (FDA) in July 2017[20,21].

Our study showed a high SVR rate after retreatment with the SOF/VEL/VOX combination (97.8%). The presence of liver cirrhosis in some of our patients within this group could have affected the SVR rate and adverse events. This group of patients had a significantly lower platelet count, serum albumin, and higher bilirubin than the other 2 groups. The POLARIS-1 and POLARIS-4 phase-3 trials reported a high safety and efficacy of the 12-week combination of SOF/VEL/VOX for retreatment of DAAs-non responders irrespective of the genotype or the RAS profile[22]. In a

large European study, Degasperi *et al.*[23] reported that liver cirrhosis and hepatocellular carcinoma were the only predictors of nonresponse to retreatment with the 12-week combination of SOF/VEL/VOX (SVR-12= 96%). They also reported that fatigue (6%), hyperbilirubinaemia (6%) and anemia (4%) were the most common adverse events. In our study, no adverse events were reported with this drug combination which may be related to the small number of patients in our study with a low incidence of adverse events. In addition, 61% of the patients of Degasperi *et al.*[23] had advanced liver fibrosis (more than or equal to F3).

Combining SOF with OMB, PAR and RIT ± RBV has shown adequate efficacy and safety for the treatment of naïve patients with HCV genotype-4[9]. This combination was also used for treatment-experienced patients. El Kassas *et al.*[9] reported an SVR-12 for retreatment using SOF/OMB/PAR/RIT/RBV to be 92.9%. They reported that this was the lowest SVR-12 among their used treatment regimens. Another study by Ismail and Wadea[24] also reported an intention-to-treat SVR-12 of 93.4%[23]. Our study showed a higher SVR-12 for this regimen, up to 99.3% in patients who completed their 12-week treatment regimens and 96.16% in all patients who received it.

El Kassas *et al.*[9] reported an SVR-12 of 100% in patients who were re-treated with the SOF/DCV/RBV combination. In our study, the response rate to this regimen was 96.2%. So far, the SOF/DCV±RBV combination has proved an adequate efficacy (SVR-12 of 94% in cirrhotic patients and 90.4% in treatment-experienced patients) and safety for the treatment of naïve and experienced Egyptian patients with CHC[24]. El-Khayat *et al.*[25] reported that the addition of RBV significantly increased SVR-12 rates. Also, the addition of RBV and prolongation of treatment duration from 12 to 16 weeks further increased the SVR-12 rates. In addition, they reported mild adverse events, mainly anemia, easy fatigability, headaches and itching due to underlying liver disease rather than the used drug.

Several causes have been proposed for the failure to achieve SVR following HCV DAAs therapy. These causes include suboptimal treatment due to inadequate selection of medications with or without a short duration of therapy[26]. HCV genotypes or subtypes also play a role, e.g., genotypes 3 and 4, particularly subtype 4r, are difficult to treat. Prior treatment with DAAs, the severity of liver affection, drug-drug interactions, and extra-hepatic manifestations of CHC and other comorbidities can impact DAAs treatment outcome. Patients with baseline resistant viral populations exceeding 10-25% of their viral quasispecies carry a reduced probability of achieving SVR[27].

According to the guidelines of the European Association for the Study of the Liver[19], the 12-week combination of SOF/VEL/VOX is the first-line therapy for DAAs-experienced patients with and without compensated cirrhosis. Patients with a low chance of achieving SVR such as those with decompensated cirrhosis, multiple DAA treatment failures or complex RAS results, may be treated with a combination of SOF/Glecaprevir/Pibrentasvir and/or the addition of weight-based RBV and/or treatment duration of 16–24 weeks. A major limitation to our study is the lack of RAS analysis and HCV genotype analysis for the included patients. We assume that the results of this study could be applied for patients with infection of HCV genotype 4, as nearly 94.1% of patients with CHC in Egypt carry the genotype 4[3].

CONCLUSION

In conclusion, SOF/VEL/VOX is well tolerated when treating the treatment-experienced patients with significantly lower adverse events and comparable efficacy compared to the studied regimens (SOF/DAC/RBV and SOF/OMB/PAR/RIT/RBV). This study may provide other retreatment options with adequate response rates for DAAs non-responders when the SOF/VEL/VOX combination is not available.

AUTHORS' CONTRIBUTIONS

Conceptualization: MS, HS; methodology: MS, RA, HD, WA; formal analysis and investigation: RA; writing, original draft preparation: HIS; writing, review, and editing: MS, RA, HD, WA; resources: RA, HD, WA; supervision: MS.

CONFLICT OF INTERESTS

All authors declare the absence of any financial or personal relationships with other people or organizations that could inappropriately influence and bias the work.

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