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Effectiveness and safety of SOF/VEL containing rescue therapy in treating chronic HCV-GT4 patients previously failed NS5A inhibitors-based DAAs

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Abstract

Background and aims NS5A inhibitors are an important option for treating chronic HCV-GT4 patients. Retreatments after NS5A-based DAAs failure are limited. We aimed to determine the effectiveness and safety of SOF/VEL-containing regimens for HCV retreatment after NS5A-regimen failure.

Methods Prospective cohort study assessing the efficacy and safety of retreatment with SOF/VEL in addition to either voxilaprevir or ribavirin in patients who had failed previous NS5A-based DAA treatment. The primary outcome was SVR12. Safety and tolerability data were collected.

Results One hundred fifty patients were included. The mean age was 53 years, 64% were male, and 50% of included patients had liver cirrhosis, with a mean FIB-4 score of 3.12 (±2.30) and Child-Turcotte-Pugh (CTP) score of 7.27 (±0.48), and failed previous SOF/DCV + RBV, they were assigned to 24 weeks of SOF/VEL + RBV. The remaining 50% of participants had no liver cirrhosis and failed previous SOF/DCV, they were assigned to 12 weeks of treatment with SOF/VEL/VOX. Overall, SVR12 was achieved by 96% ($n = 144/150$) of included patients; 97.33% for SOF/VEL/VOX and 94.67% for SOF/VEL/RBV. Thirty-one patients experienced mild AEs; the most commonly reported mild AE in the SOF/VEL + RBV group was hyperbilirubinemia ($n = 9$) whereas in the SOF/VEL/VOX group were headache ($n = 4$) and vertigo ($n = 4$). Only one patient in SOF/VEL + RBV reported moderate treatment-related AE in the form of anemia and no reported severe AE.

Conclusion Retreatment of non-cirrhotic patients with 12 weeks SOF/VEL/VOX and treatment of cirrhotic patients with 24 weeks with SOF/VEL + RBV after the failure of first-line NS5A-based therapy was an effective and well-tolerated treatment option.

Keywords Rescue, Failure, Genotype 4

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Introduction

Globally, the World Health Organization (WHO) estimates that approximately 58 million people have chronic hepatitis C virus (HCV) infection, and approximately 1.5 million new infections occur each year, according to their estimates in 2022 [1]. Egypt is considered among the highest burden of cases because of its high overall population, high prevalence, or both [2].

A number of recent studies have verified the remarkable effectiveness of treating chronic HCV with direct-acting antiviral therapy (DAA) and the consequent notable amelioration of hepatic fibrosis [3, 4].

Although treatment with DAA has been enormously successful, there is a small percentage of patients who have not achieved sustained virological response (SVR) despite DAA treatment and therefore will require retreatment therapy. It is possible that prior exposure to the DAA may result in the selection of resistance-associated substitutions (RASs), particularly for NS5A inhibitors, and therefore the retreatment regimen may be compromised theoretically [5].

NS5A inhibitors are the most potent DAAs. However, they present relatively low barriers to resistance in comparison with other classes, such as non-nucleotide HCV NS5B inhibitors (6), Further, substitutions associated with NS5A inhibitors resistance are usually persistent for an extended period of time [6, 7].

The current international guidelines [8, 9] recommend 12 weeks of retreatment with sofosbuvir (SOF)/velpatasvir (VEL)/voxilaprevir (VOX). More than 95% of individuals who had been exposed to DAA achieved SVR with the second-generation regimen SOF/VEL/VOX, whereas RASs had no effect on the outcome of treatment. It is not clear whether ribavirin can be useful as an additional treatment in these cases of treatment failure. In patients with HCV genotype 3 and cirrhosis, SOF/VEL/VOX was slightly less efficacious, and such recommendations are based on only a small number of patients treated [10, 11].

This study aims to provide real-life data regarding the effectiveness and safety of SOF and VEL-containing regimens for retreatment of chronic HCV after NS5A inhibitors-regimen virological failure in Egyptian HCV GT4 patients.

Patient and methods

Study design

This is a prospective cohort study evaluating the efficacy and safety of sofosbuvir and velpatasvir with either voxilaprevir or ribavirin for retreatment of chronic HCV-infected patients who failed treatment with sofosbuvir, daclatasvir with or without ribavirin regimen in routine clinical practice at Embaba Fever Hospital, specialized viral hepatitis treatment center, affiliated to the National Committee for Control of Viral Hepatitis (NCCVH), Cairo, Egypt.

The inclusion criteria were adults (>18 years) with chronic hepatitis C without cirrhosis or with cirrhosis (Child A/B) who had previously failed combined therapy with sofosbuvir and daclatasvir regimen from September 2019 to September 2020. Patients who met any of the following criteria at enrollment were excluded: (1) Child-Turcotte-Pugh (CTP) score > 8, (2) platelets < 50,000/μL, (3) coinfection with HBV or HIV, (4) pregnancy, (5) hepatocellular carcinoma, except 6 months after intervention aiming at cure with no evidence of activity by dynamic imaging (CT or MRI), (6) Extrahepatic malignancy except after 2 years of disease-free interval. In the case of lymphomas and chronic lymphocytic leukemia, treatment can be initiated immediately after remission based on the treating oncologist's report.

Patients were stratified into two groups:

1- Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) group contains patients without cirrhosis, those patients received a fixed-dose oral tablet containing 400 mg of sofosbuvir, 100 mg of velpatasvir, and 100 mg of voxilaprevir without ribavirin once daily for 12 weeks.
2- Sofosbuvir/velpatasvir + ribavirin (SOF/VEL + RBV) group contains patients with liver cirrhosis and a Child score of 8 or less; they received a fixed dose oral tablet containing 400 mg of sofosbuvir and 100 mg of velpatasvir once daily plus ribavirin 200 mg tablet three tablets per day orally this regimen for 24 weeks.

The primary endpoint was the percentage of patients who achieved a sustained virological response (SVR12), which is defined as HCV PCR remaining undetectable at week 12 following treatment completion. Adverse events related to the treatment were the secondary endpoint.

Measurements

Patients were assessed for baseline demographics, comorbidities, disease characteristics, prior treatments, and response types. The presence of or absence of liver cirrhosis was evaluated by liver echotexture on abdominal ultrasound and FIB-4 (< 1.45 = no or minimal fibrosis, > 3.25 = cirrhosis) and for those, with liver cirrhosis, the Child-Turcotte-Pugh score (CTP) was recorded at the start of treatment. Laboratory tests included complete blood count (CBC), liver biochemical profile, international normalization ratio, creatinine, alfa fetoprotein, and HCV PCR level.

During the treatment period and over a 12-week post-treatment follow-up, patients were evaluated every 4 weeks for clinical symptoms and adverse events with a special focus on serious adverse effects that led to hospital admissions or deaths, and severe conditions, such as HCC or the need for liver transplants. CBC, ALT, and AST were repeated every 4 weeks during the treatment period. HCV PCR level was measured at the end of treatment (EOT) visit and 12 weeks after the treatment completion visit using the COBAS AmpliPrep/COBAS TaqMan (using the COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test, version 2.0, with a lower limit of quantification of 20 IU/ml). In terms of virological response, patients were considered "responders" if they had HCV RNA undetectable at the SVR12 time point using a sensitive quantification assay (< 20 IU) and considered "failure" if they experienced reappearance of HCV RNA at any time during or after treatment.

Adverse drug events were classified according to their severity into the following:

- Mild adverse events: transient events didn't interrupt treatment
- Moderate adverse events: interrupt treatment or require hospitalization
- Severe adverse events: death as a result of treatment when other causes of death rolled out.

The study was conducted in accordance with Good Clinical Practice Guidelines and was approved by the institutional review board. The patient consented to the registries' storage of their anonymous data.

Statistical analysis

With a sample of 75 subjects per group, we had 80% power to detect a difference of 15% between the null hypothesis that the proportion of SVR12 in patients receiving velpatasvir is 80% in each group and the alternative hypothesis that the proportion of SVR12 among patients receiving velpatasvir is 95% based on previous literature with a significance level of 0.05 using a two-sample test of proportions. Student's *t*-test was used to compare normally distributed quantitative variables, expressed as mean ± standard deviation. The median and interquartile range of variables with non-normal distributions were calculated using the Mann–Whitney *U* test. The frequencies and percentages of categorical variables were compared using the chi-square or Fisher exact tests, as appropriate, and are presented as percentages and frequencies. *P* values < 0.05 were considered statistically significant. All analyses were carried out using the 2015 StataCorp. Stata Statistical Software, release 14 (StataCorp LP; College Station, TX, USA).

Results

Patient population

In total, 150 patients were included: 64% ($n=96$) were men, the median age was 53 (± 13) years with a significantly older age of SOF/VEL + RBV group in comparison SOF/VEL/VOX group (55.07 ± 11.97 Vs. 50.53 ± 12.79, $p=0.03$), 20 (13.33%) had hypertension and 35 (23.33%) had diabetes. Forty-four (29.33%) patients were smokers but none of the included patients was alcoholic or intravenous drug abuser (IVDU). All patients within SOF/VEL + RBV group had liver cirrhosis with a mean FIB-4 score of 3.12 (± 2.30) and Child-Turcotte-Pugh (CTP) score of 7.27 (± 0.48). All patients had previously experienced a sofosbuvir-based interferon-free regimen with the following combinations; all patients within the SOF/VEL/VOX group had previously received sofosbuvir combined with daclatasvir whereas all patients with SOF/VEL/RBV group had previously received sofosbuvir

Table 1 Baseline demographic and clinical data

Variable	All cohort	SOF/VEL + RBV *n* = 75	SOF/VEL/VOX *n* = 75	*P* value
Mean age (year)	52.8 ± 12.55 23–82	55.07 ± 11.97	50.53 ± 12.79	0.03
Male gender (%)	96(64)	41 (54.67)	55 (73.33)	0.02
Urban residency	96 (64)	36 (48)	60 (80)	< 0.001
Treatment experienced				NA
- SOF/DCV	- 75 (50)	- 0	- 75 (100)	
- SOF/DCV/RBV	- 75 (50)	- 75 (100)	- 0	
Smoking	44 (29.33)	8 (10.67)	36 (48)	< 0.001
History of hypertension	20 (13.33)	9 (12)	11 (14.67)	0.63
History of DM	35 (23.33)	16 (21.33)	19 (25.33)	0.56
Con-meds	9	0	9 (100)	NA

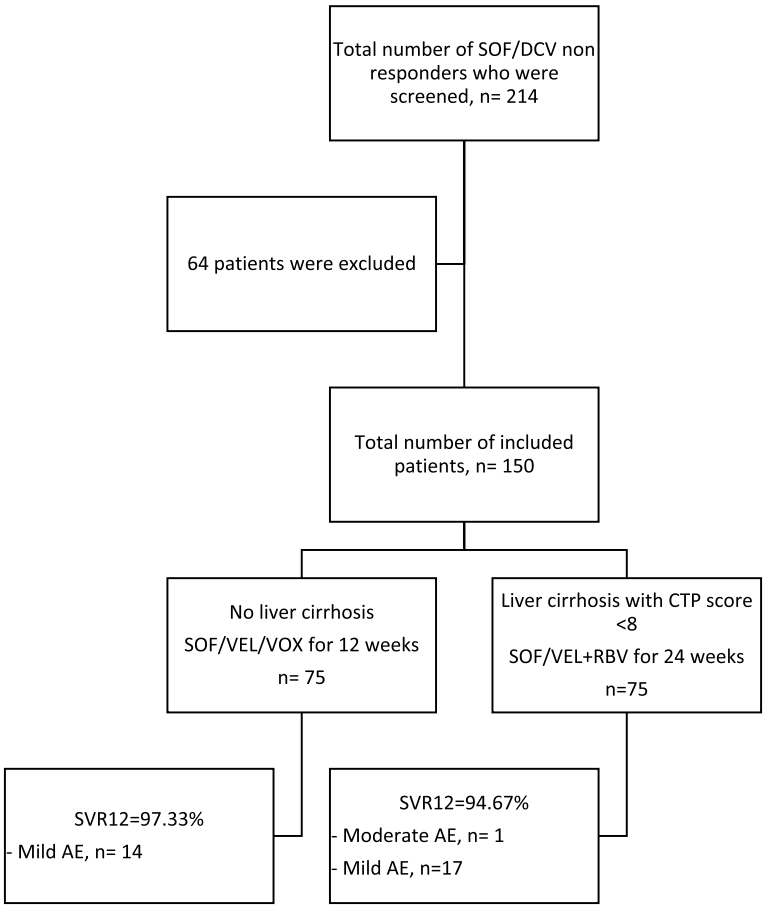

Fig. 1 Patients disposition

Table 2 Baseline laboratory data

Variables	All patients *n* = 150	SOF/VEL + RBV *n* = 75	SOF/VEL/VOX *n* = 75	*P* value
Hemoglobin (g/L)	13.36 ± 1.68	12.98 ± 1.77	13.75 ± 1.51	**0.01**
W.B.C (10^3/mm^3)	5.86 ± 2.25	5.36 ± 2.09	6.36 ± 2.31	**< 0.001**
Platelets (10^3/mm^3)	175 ± 76	119 ± 41	232 ± 58	**< 0.001**
ALT (U/L)	57 ± 36	63 ± 36	50 ± 36	0.03
AST (U/L)	60 ± 34	77 ± 36	43 ± 22	**< 0.001**
Albumin (g/dL)	3.76 ± 0.69	3.25 ± 0.53	4.27 ± 0.40	**< 0.001**
Bilirubin (umol/L)	1.07 ± 0.67	1.43 ± 0.75	0.71 ± 0.30	**< 0.001**
INR	1.42 ± 0.41	1.73 ± 0.36	1.1 ± 0.09	**< 0.001**
Creatinine (umol/L)	0.80 ± 0.25	0.71 ± 0.27	0.89 ± 0.20	**< 0.001**
Random glucose (mmol/L)	127 ± 61	122 ± 51	132 ± 70	0.31
HCV PCR (log10)	5.20 ± 1.38	5.24 ± 1.21	5.17 ± 1.54	0.74
FIB-4	3.12 ± 2.30	4.79 ± 2.12	1.45 ± 0.78	**< 0.001**
Cirrhosis (yes)	75 (50%)	75 (100)	0	NA
Mean CTP score if cirrhotic	7.27 ± 0.48	7.27 ± 0.48	0	NA

combined with daclatasvir and ribavirin (Table 1 and Fig. 1).

At baseline, patients within the SOF/VEL/VOX group tended to have significantly better hematological and liver biochemical parameters in comparison to those within SOF/VEL/RBV group as shown in Table 2. At the end of treatment (EOT) time point, patients within SOF/VEL/VOX group showed a significant decrease in baseline hemoglobin (13.15 ± 1.33 vs. 13.75 ± 1.51, $p = < 0.001$), albumin levels (4.11 ± 0.45 vs. 4.27 ± 0.40, $p = 0.02$) and necro-inflammatory markers (ALT 32 ± 11 vs. 50 ± 36, $p = < 0.001$, AST; 27 ± 9 vs. 43 ± 22, $p = < 0.001$) and significant increase in baseline bilirubin (0.86 ± 0.24 vs. 0.71 ± 0.30, $p = < 0.001$). Patients received SOF/VEL + RBV showed significant decrease in baseline hemoglobin (11.39 ± 1.34 vs. 12.98 ± 1.77, $p = < 0.001$), ALT (34 ± 11 vs. 63 ± 36, $p = < 0.001$), AST (30 ± 12 vs. 77 ± 36, $p = < 0.001$), and bilirubin (1.02 ± 0.25 vs. 1.43 ± 0.75, $p = < 0.001$) and significant increase in baseline albumin (3.60 ± 0.39 vs. 3.25 ± 0.53, $p = < 0.001$) at EOT time-point as demonstrated in Table 3.

All patients completed therapy and achieved EOT response and were followed for 12 additional weeks. The overall sustained virological response at post-treatment week 12 (SVR12) was achieved in 96% ($n = 144/150$) of included patients; 97.33% ($n = 73/75$, 95% confidence interval 91–100%) of SOF/VEL/VOX group and 94.67% ($n = 71/75$, 95% confidence interval 87–99%) of SOF/VEL + RBV group, with no significant difference between both groups ($p = 0.41$). Characteristics of patients who did not achieve SVR12 are shown in Table 4.

Within the SOF/VEL/VOX group, only 14 (18.34%) mild adverse episodes were reported during treatment that were transient and did not interrupt treatment or require hospitalization. Headache ($n = 4$) and vertigo ($n = 4$) were the most common, followed by abdominal colic ($n = 2$), thrombocytopenia ($n = 1$), hair loss ($n = 1$), vomiting ($n = 1$), and arthralgia ($n = 1$). Moderate and severe adverse events were not reported in the group of patients. Within the SOF/VEL + RBV group, only a single moderate adverse event was reported in the form of anemia (hemoglobin < 8.5) that required a stop of ribavirin therapy and blood transfusion, and 17(22.67%) mild adverse episodes were reported during treatment. Hyperbilirubinemia ($n = 9$) was the most common, followed by anemia ($n = 3$), headache ($n = 1$), abdominal colic ($n = 1$), thrombocytopenia ($n = 1$), easy fatiguability ($n = 1$), and dark skin ($n = 1$). No reported severe treatment-related adverse events (Table 5).

Discussion

The present study included 150 chronic HCV patients who experienced virological failure to NS5A inhibitors containing anti-HCV regimen namely SOF + DCV

Table 3 Changes in laboratory data at the end of treatment in comparison to its baseline according to the treatment regimen

Variables	SOF/VEL + RBV ($n = 75$)		*P* value	SOF/VEL/VOX ($n = 75$)		*P* value
	Baseline	EOT		Baseline	EOT	
Hemoglobin (g/L)	12.98 ± 1.77	11.39 ± 1.34	**< 0.001**	13.75 ± 1.51	13.15 ± 1.33	**< 0.001**
W.B.C (10^3/mm^3)	5.36 ± 2.09	6.48 ± 4.41	0.07	6.36 ± 2.31	5.81 ± 1.51	0.06
Platelets (10^3/mm^3)	119 ± 41	167 ± 49	**< 0.001**	232 ± 58	236 ± 64	0.57
ALT (U/L)	63 ± 36	34 ± 11	**< 0.001**	50 ± 36	32 ± 11	**< 0.001**
AST (U/L)	77 ± 36	30 ± 12	**< 0.001**	43 ± 22	27 ± 9	**< 0.001**
Albumin (g/dL)	1.43 ± 0.75	1.02 ± 0.25	**< 0.001**	0.71 ± 0.30	0.86 ± 0.24	**< 0.001**
Bilirubin (umol/L)	3.25 ± 0.53	3.60 ± 0.39	**< 0.001**	4.27 ± 0.40	4.11 ± 0.45	**0.02**

Table 4 Characteristics of non-SVR12 patients, $n = 5$

Treatment received	Age (years)	Gender	Smoking	Alcohol use	Comorbid	Previous treatment	HCV viral load (IU)	Liver cirrhosis	FIB-4
SOF/VEL/VOX	41	Male	Yes	No	HTN	SOF/DCV	74	No	0.76
SOF/VEL/VOX	36	Male	Yes	Yes	none	SOF/DCV	179	No	1.17
SOF/VEL + RBV	65	Male	Yes	No	DM	SOF/DCV + RBV	3680	Yes	4.99
SOF/VEL + RBV	56	Female	No	No	HTN	SOF/DCV + RBV	1,004,000	Yes	3.62
SOF/VEL + RBV	56	Female	No	No	HTN + DM	SOF/DCV + RBV	6,220,000	Yes	4.24
SOF/VEL + RBV	59	Female	No	No	None	SOF/DCV + RBV	281,000	Yes	2.79

[a] *SOF* sofosbuvir *VEL* velpatasvir, *VOX* voxilaprevir, *DCV* daclatasvir, *RBV* ribavirin

Table 5 Reported adverse events among the study cohort

	SOF/VEL + RBV (*n* = 75)	SOF/VEL/VOX (*n* = 75)
Mild adverse events		
Headache	1	4
Vertigo	0	4
Abdominal colics	1	2
Thrombocytopenia	1	1
Hair loss	0	1
Vomiting	0	1
Arthralgia	0	1
Hyperbilirubinemia	9	0
Anemia	3	0
Easy fatiguability	1	0
Dark skin	1	0
Moderate adverse events		
Anemia	1	0

with or without additional ribavirin. Patients were retreated with SOF + VEL with either VOX for 12 weeks or RBV for 24 weeks. Overall, 96% (*n* = 144/150) of included patients attained SVR12 to retreatment; 97.33% (*n* = 73/75) for SOF/VEL/VOX and 94.67% (*n* = 71/75) for SOF/VEL + RBV. The overall relapse rate was 4%; for the SOF/VEL/VOX group was 1.3% and for the SOF/VEL + RBV group was 2.7%. Among our study group, 31 patients experienced mild adverse events, 1 patient in SOF/VEL + RBV reported moderate treatment-related adverse events in the form of anemia, and no reported severe adverse events.

In Egypt, infection with HCV genotype 4 particularly subtype 4a is the most prevalent [12]. A direct-acting antiviral targets specific nonstructural viral proteins, so it disrupts viral replication [4], a successful viral eradication results in a significant reduction in liver fibrosis [3]. The overall efficacy of DCV plus SOF with or without ribavirin in treating Egyptian patients with HCV-GT4 was estimated at > 95% [13, 14]. Virus, host, and drug factors have been implicated in DAA failures. However, a causal relationship has not been established between these factors and the response to DAA [15, 16]. Generally, treatment failure is associated with the selection of HCV RASs, which are viral variants that are less sensitive to the DAA(s) used [17–20].

The frequency of RASs at the time of DAA treatment failure has been reported to range between 50 and 90% according to several studies. SOF has a high genetic barrier [21–27], the frequency of SOF-resistant nucleotide NS5B RASs ranges from 1 to 3%, and high-level resistant RASs disappear shortly after being introduced to the cell since these variants have high fitness costs in the absence of DAAs. As a result, these RASs quickly reverted back to the wild type since they cannot efficiently replicate. It is accepted practice to include SOF retreatment regimens after DAA virological failure, which might enhance patient response to therapy [28].

Previous exposure to NS5A inhibitors can lead to the emergence of NS5A inhibitors RASs that persist for a long period of time as they do not compromise the replication fitness [6, 7, 29, 30]. The selection of high-level resistant NS5A inhibitors RASs following DAA failure reduced the effectiveness of first-generation rescue therapy, especially in the absence of DAA classes changing [31–33].

In the current study, 75 patients who failed treatment with SOF/DCV were treated with 12 weeks of SOF/VEL/VOX, the SVR12 rate was 97.33% (*n* = 73/75). After the failure of first-generation DAA, SOF/VEL/VOX, a second-generation DAA regimen, is currently recommended for pangentopic retreatment [11, 34]. Our SVR12 rate was comparable to that reported for GT1 infected patients (222/228; 97% SVR) in POLARIS-1 and POLARIS-4 phase-II and III studies [11]. Our results align with that reported by Belperio et al. who reported an SVR12 rate of 100% for GT4 (12/12) (37, and that reported in RCT by El-Kassas et al. as an SVR12 rate of 97.9% (138/141) for intention to treat group [35].

The SVR12 rate was 94.67% (*n* = 71/75) in our 75 chronic HCV -GT4 patients with liver cirrhosis who failed previous SOF/DCV + RBV and were treated with SOF/VEL + RBV for 24 weeks. The addition of weight-based ribavirin to SOF/VEL in the treatment regimen of patients with compensated cirrhosis was supported by clinical trials [11, 36] and real-world studies [37–40]. Additionally, the FDA released a warning in 2019 regarding infrequent instances of hepatic decompensation, which included liver failure and fatalities in patients receiving NS3/4A protease inhibitors for CTP classes B and C. Three of these cases involved using sofosbuvir/velpatasvir/voxilaprevir [41–44]. A clinical study on genotype 3 showed that of the 9 cirrhotic patients treated with SOF/VEL + RBV, 8 (89%) achieved SVR12 [37]. Gen et al. reported SVR12 of 83% (5/6) in GT1 and 75% (9/12) in GT3 patients treated for 24 weeks with SOF/VEL + RBV after prior NS5A inhibitors-based HCV treatment failure [38].

Twelve weeks of treatment with SOF/VEL/VOX was efficient and well tolerated, and 14 patients reported mild adverse events (headache, vertigo, abdominal colic, thrombocytopenia, hair loss, vomiting, and arthralgia). No moderate or severe adverse events were reported in this patient group.

The overall safety of SOF/VEL + RBV for 24 weeks was acceptable, only one patient reported moderate adverse event in the form of anemia, and 17 patients reported mild adverse events (hyperbilirubinemia, anemia, headache, abdominal colic, thrombocytopenia, fatigue, and dark urine) and no severe adverse events were reported. This regimen was safe and well tolerated, and ribavirin showed a safety profile consistent with what was previously known about it [39].

Limitations to this work include a small sample size and lack of bassline HCV genotype testing. However, nearly 94% of Egyptian patients with HCV are infected by HCV GT4 [40, 45, 46]. The lack of baseline RAS testing is another limitation.

Conclusion

Retreatment of non-cirrhotic patients with 12 weeks SOF/VEL/VOX and treatment of cirrhotic patients with 24 weeks with SOF/VEL + RBV after the failure of first-line NS5A inhibitors-based therapy was an effective and well-tolerated treatment option.

Authors' contributions

All authors contributed equally to the manuscript, and read and approved the final manuscript.

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None.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with Good Clinical Practice Guidelines and was approved by the institutional review board. The patient consented to the registries' storage of their anonymous data.

Competing interests

The authors declare that they have no conflct of interest.

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