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BRIEF REPORT

# High success rates for the use of sofosbuvir/ombitasvir/paritaprevir/ritonavir + ribavirin and sofosbuvir/simeprevir/daclatasvir + ribavirin in retreatment of chronic hepatitis C infection after unsuccessful sofosbuvir/daclatasvir therapy: a real-life experience

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## Abstract

The aim of this work was assessment of the efficacy and tolerability of two different regimens for retreatment of hepatitis C virus (HCV) patients who failed to respond to SOF/DCV-based therapy. This prospective study included 104 HCV patients who failed to respond to SOF/DCV-based therapy. Patients were randomly allocated to two groups. Efficacy and tolerability were assessed. The 12-week sustained virological response (SVR12) rates were 96% and 94.4% in groups B and A, respectively, with no significant difference ($p = 1.000$). Most adverse events reported were mild to moderate, with no deaths during the study. Multi-target direct-acting antiviral (DAA) combinations are efficient for retreatment of HCV patients after failure of SOF/DCV-based therapy in real-world management.
ClinicalTrials.gov identifier: NCT02992457.

## Introduction

Hepatitis C virus (HCV) infection is one of the most prevalent causes of chronic hepatitis worldwide, with an estimated 71 million people who have chronic hepatitis C virus infection. It is a leading cause of severe liver disease and liver cancer in several countries [1, 2]. Egypt is one of the countries with the highest prevalence of chronic hepatitis C (CHC), with about 4.4% of the population aged 1-59 years having an active HCV infection [3–6].

Diagnosis of CHC is based on detection of anti-HCV antibodies. Confirmation of active CHC relies mainly on direct detection of HCV genomic RNA [7]. The endpoint of CHC therapy is viral clearance and achievement of a sustained virological response (SVR), which is defined as undetectable HCV RNA at 12 weeks after the end of treatment [8]. Understanding structure, life cycle and replication mechanism of HCV has opened the door to development of direct-acting antiviral agents (DAAs) that directly inhibit target viral proteins [9].

The high rates of SVR achieved using DAAs has triggered a major revolution in HCV treatment, replacing the old interferon (IFN)-based therapy that had been the standard of care in CHC for many years. Currently, several DAA regimens for treatment of CHC are approved, including pangenotypic regimens. These oral IFN-free regimens all show excellent efficacy and tolerability profiles and accordingly offer a unique opportunity to achieve HCV elimination [10].

In 2006, Egypt established the National Committee for the Control of Viral Hepatitis (NCCVH), which took the lead in HCV management via a large nationwide network of centers for specialized viral hepatitis treatment. Due to consequent changes in international HCV treatment guidelines and the availability of DAAs, the Egyptian practice

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guidelines were repeatedly modified [11]. In view of the available data that more than 90% of Egyptian patients with HCV have genotype 4, the NCCVH treatment protocol for CHC relies on the combination of sofosbuvir (SOF) plus daclatasvir (DCV) with or without ribavirin (RBV) as the main treatment regimen. On large-scale application, the SOF/DCV-based regimens were well tolerated and yielded SVR rates of about 95% in Egyptian CHC patients [12].

Despite the high success rates accompanying DAAs use, treatment failures attributed to several host, drug, and virus-related factors still occur in a substantial number of treated patients (1-15%) and still represent a problematic issue [13].

Retreatment after DAA failure is a challenge, especially in those for whom a non-structural protein 5A (NS5A)-based regimen failed because of the persistence of NS5A resistance-associated substitutions (RASs) that convey viral resistance up to 96 weeks after treatment failure [14]. The current updates of the international HCV treatment guidelines recommend a single-tablet combination of SOF plus velpatasvir and voxilaprevir (SOF/VEL/VOX) for 12 weeks as the standard treatment after failure of NS5A-based regimens. Addition of RBV or extension of the treatment duration of the SOF/VEL/VOX regimen as well as combining SOF with glecaprevir and pibrentasvir (GLE/PIB) could be considered in difficult-to-treat patients [15, 16].

Due to the limited availability of some newer DAAs in Egypt, the NCCVH recommends treatment of CHC patients for whom previous SOF/DCV-based regimens have failed with a combination of either SOF plus ritonavir boosted with paritaprevir and ombitasvir (OBV/PTV/r) ± RBV, or SOF plus simeprevir (SMV) and DCV ± RBV for 12 or 24 weeks according to RBV eligibility [17].

## Patients and methods

This prospective observational study was conducted on 104 CHC patients who failed to respond to SOF/DCV-based regimens and attended a major hepatitis C virus treatment center in the period from March to November 2018.

The study protocol was approved by the ethical committee of a major university hospital, and informed written consent was obtained from all patients participating in this study. The study was registered on clinicaltrials.gov (ClinicalTrials.gov identifier: NCT02992457).

Patients included in this study were adults (≥ 18 years) of both sexes with CHC and detectable HCV RNA 12 weeks after completion of an SOF/DCV-based regimen and were eligible for antiviral therapy as recommended by the Egyptian NCCVH treatment protocol (December 2016). All patients with decompensated cirrhosis (grade B and C by modified Child-Turcotte-Pugh CTP score), platelet count less than 50000/mm$^3$, hepatocellular carcinoma (except after 6 months of intervention aiming at a cure with no evidence of tumoral activity confirmed by a dynamic study), an extrahepatic malignancy (except after a 2-year disease-free interval, in the a case of lymphomas and chronic lymphocytic leukemia treatment can be initiated immediately after remission based on treating oncologist report), pregnancy or inability to use an effective contraceptive method, or inadequately controlled diabetes mellitus were excluded from the study.

The clinical/pathological data of patients were recorded, including age, sex, complete medical history, thorough clinical examination, HCV RNA quantitative PCR (polymerase chain reaction), biochemical liver function tests, complete blood count (CBC), serum creatinine, alpha fetoprotein level (AFP), hepatitis B virus surface antigen (HBsAg) and serum beta human chorionic gonadotropin for females in the child-bearing period.

Pelvi-abdominal ultrasound examination was performed for all patients at baseline and 12 weeks after the end of treatment. The severity of liver disease was assessed based on the modified CTP score.

As the applied treatment protocol allows for the use of both regimens, enrolled patients were allocated to one of the two regimens: group A included the first 54 patients, who received a combination of SOF (one tablet, 400 mg) with two co-formulated tablets of OBV/PTV/r (12.5 mg/75 mg/50 mg) and RBV for 12 weeks, and group B included the next 50 patients, who received a combination of SOF (one tablet, 400 mg), SMV (one tablet, 150 mg), DCV (one tablet, 60 mg) and RBV for 12 weeks. Patients were randomly assigned to one of the treatment groups centrally by the National Committee for Control of Viral Hepatitis.

The recommended RBV starting dose was 600 mg/day, reaching 1000 or 1200 mg/day based on patient's body weight and tolerance.

Laboratory assessments during follow up included CBC, liver transaminases, serum total bilirubin, and serum creatinine at week 4 and 8 during treatment and at the end of treatment. Assessment of the AFP level was done at baseline and 12 weeks after the end of treatment.

Treatment efficacy was assessed by achievement of SVR12, defined as undetectable HCV RNA by PCR 12 weeks after the end of treatment.

Safety and tolerability were evaluated through reporting of adverse events (AEs) and monitoring of laboratory abnormalities related to the study drugs. AEs and laboratory abnormalities were categorized according to severity based on Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [18].

### Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 18.0, IBM Corp., Chicago, USA, 2009. Descriptive statistics were done for quantitative data as the minimum and maximum of the range as well as mean ± SD (standard deviation) for quantitative normally distributed data, and for qualitative data, as number and percentage.

Inferential analysis was done for quantitative variables using the Shapiro-Wilk test for normality testing, independent *t*-test in cases of two independent groups with normally distributed data, repeated-measure ANOVA test (RMANOVA) for analysis of more than one time point with normal distribution. For qualitative data, inferential analysis for independent variables was done using the chi square test for differences between proportions and Fisher's exact test for variables with small expected numbers. Differences were considered significant when the *P*-value was less than 0.5.

## Results

### Study population

One hundred four patients were enrolled in this study and were allocated to two groups. Group A (n = 54) received a combination of SOF plus OBV/PTV/r + RBV, and group B (n = 50) received a combination of SOF/SMV/DCV + RBV.

The demographic and basal characteristics were matched between the two groups. There were more males than females in each group (61.1% and 60% in group A and B, respectively). The age of the patients was matched in both groups (mean ± SD = 51.5 ± 10.7, 51.5 ± 10.9 years for group A and B, respectively, $p = 0.992$).

Regarding DAA experience before enrollment in the current study, in group A, 33 patients out of 54 (61.1%) were SOF/DCV-experienced, while 21 patients were SOF/DCV/RBV-experienced. In group B, 26 patients out of 50 (52%) were SOF/DCV-experienced, while 24 patients were SOF/DCV/RBV-experienced. Patients' demographics and basal characteristics are summarized in Table 1.

### Outcomes

No significant difference in SVR rates was observed between the study groups. The SVR12 rate was 94.4% (51/54 patients) in group A and 96% (48/50 patients) in group B ($p = 1.000$). Regarding safety and tolerability, both regimens were generally safe and well tolerated, with no deaths due to AEs. Among all of the study patients, only one patient in group B discontinued treatment after 4 weeks due to hepatic decompensation in the form of significant elevation of serum total bilirubin (6.4 mg/dl) and development of ascites; surprisingly, this patient achieved SVR12.

Reported AEs were generally mild to moderate (grade 1 or 2 severity) in both study groups; however, dermatological AEs were significantly more frequent in group B patients ($p = 0.005$), and headache was significantly more frequent in group A patients ($p = 0.032$).

In group A patients, the most commonly reported AEs were fatigue (29.6%), headache (20.4%), abdominal pain (18.5%), and musculoskeletal pain (14.8%). While in group B patients, the most commonly reported AEs were fatigue (28%), photosensitivity (14%), itching (14%), and abdominal pain (10%). The reported AEs related to treatment are listed in Fig. 1.

### Laboratory abnormalities

A clinically significant drop in the hemoglobin level was observed in both study groups during treatment; however,

**Table 1** Demographic and basal characteristics of the studied groups

| Variable | | Group A (n = 54) | Group B (n = 50) | *P* |
|---|---|---|---|---|
| Age (years) | Mean ± SD | 51.5 ± 10.7 | 51.5 ± 10.9 | ^0.992 |
| Sex (n, %) | Male | 33 (61.1%) | 30 (60.0%) | #0.908 |
| | Female | 21 (38.9%) | 20 (40.0%) | |
| Tobacco smoking (n, %) | | 14 (25.9%) | 17 (34.0%) | #0.368 |
| IV drug addiction (n, %) | | 2 (3.7%) | 0 (0.0%) | &0.496 |
| Alcohol consumption (n, %) | | 0 (0.0%) | 0 (0.0%) | – |
| Hypertension (n, %) | | 8 (14.8%) | 5 (10.0%) | #0.458 |
| DM (n, %) | | 17 (31.5%) | 15 (30.0%) | #0.870 |
| Previous HCV treatment | SOF/DCV | 33 (61.1%) | 26 (52.0%) | #0.349 |
| | SOF/DCV/RBV | 21 (38.9%) | 24 (48.0%) | |
| HCV RNA ($\times 10^3$/mL) | Mean ± SD | 631.6 ± 986.0 | 787.8 ± 1080.1 | ^0.782 |

^, independent *t*-test; #, chi square test; &, Fisher's exact test

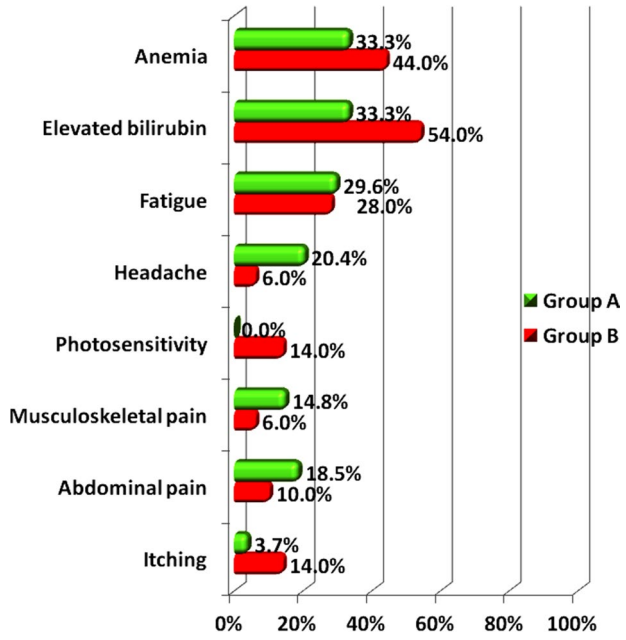


**Fig. 1** Side effects of treatment in the studied groups

there was no. statistically insignificant difference between both groups (33.3% and 44% in group A and B respectively, $p=0.264$). The hemoglobin drops were mostly of grade 1 or 2 severity except for one patient in group A who suffered a severe (grade 3) drop in hemoglobin (7.0 g/dl) that might have been induced by RBV.

Clinically significant hyperbilirubinemia was observed in both study groups during treatment. In addition, significantly higher total bilirubin levels were observed in group B than in group A at week 4 of treatment (54% versus 33.3%, mean ± SD = 1.1 ± 0.6 and 1.4 ± 0.9 mg/dl in group A and B respectively, $p=0.031$). However, the elevation in total bilirubin among all study patients was generally mild to moderate (grade 1 or 2), except for two patients, one in each group who suffered severe (grade 3) hyperbilirubinemia (4.2 and 6.4 mg/dl). A comparison of the changes in hemoglobin and serum total bilirubin levels during treatment between the study groups is shown in Table 2.

## Discussion

Chronic hepatitis C virus infection remains a major health concern worldwide, especially in countries with high prevalence like Egypt [1]. Introduction of new DAAs-based therapies is certainly one of the most clinically significant breakthroughs in recent medical history [11].

Despite the high success rates accompanying DAAs use, treatment failures still occur in substantial numbers of treated patients. Retreatment after DAAs failure is a challenge, especially for those who failed to respond to an NS5A-based regimen, which may be attributed to persistence of NS5A RASs for long periods and the occurrence of cross-resistance to different NS5A inhibitors. In addition, the limited availability of some recently approved DAAs in some countries (as in the Egyptian situation) augments this challenge [13, 14].

The current updated CHC treatment guidelines recommend the combination of SOF/VEL/VOX for 12 weeks as the standard treatment after failure of NS5A-based regimens. Another alternative in very difficult-to-cure patients is a combination of either SOF/VEL/VOX or SOF plus GLE/PIB, which should be used with the addition of RBV and/or extension of treatment duration in such patients [15, 16].

Due to the limited availability of some newer DAAs in Egypt, the NCCVH recommends treatment of patients who failed to respond to SOF/DCV-based regimens with a combination of SOF plus OBV/PTV/r ± RBV, or SOF/SMV/DCV ± RBV for 12 or 24 weeks according to RBV eligibility [17].

**Table 2** Changes in hemoglobin (gm/dL) and serum total bilirubin (mg/dL) during treatment

| Time | | Measure | Group A (n = 54) | Group B (n = 50) | ^*P* |
|---|---|---|---|---|---|
| Week 0 | Hemoglobin | Mean ± SD | 13.9 ± 1.6 | 14.0 ± 1.7 | 0.918 |
| | Total bilirubin | Mean ± SD | 0.8 ± 0.4 | 0.8 ± 0.3 | 0.968 |
| Week 4 | Hemoglobin | Mean ± SD | 12.6 ± 1.7 | 12.6 ± 1.6 | 0.964 |
| | Total bilirubin | Mean ± SD | 1.1 ± 0.6 | 1.4 ± 0.9 | **0.031*** |
| Week 8 | Hemoglobin | Mean ± SD | 12.4 ± 1.7 | 12.5 ± 1.4 | 0.694 |
| | Total bilirubin | Mean ± SD | 1.1 ± 0.7 | 1.2 ± 0.7 | 0.420 |
| Week 12 | Hemoglobin | Mean ± SD | 12.1 ± 1.6 | 12.3 ± 1.4 | 0.460 |
| | Total bilirubin | Mean ± SD | 1.2 ± 0.6 | 1.1 ± 0.5 | 0.744 |
| #*P* | | | **< 0.001*** | **< 0.001*** | |

^, independent *t*-test (comparison between groups)

#, RMANOVA (comparison between times)

*, significant

The aim of this study was to evaluate the efficacy and tolerability of the two standard regimens recommended by the Egyptian NCCVH for treatment of CHC patients who fail to respond to SOF/DCV-based regimens.

The demographic and basal characteristics were matched between the two study groups. Males were more common than females in both groups (61.1% and 60% in group A and B, respectively). The age of patients was matched in both groups (year, mean ± SD = 51.5 ± 10.7, 51.5 ± 10.9 years for group A and B, respectively, $p = 0.992$). Baseline demographics and basal characteristics were matched to those reported by Abdel-Moneim et al. who used a combination of SOF plus OBV/PTV/r + RBV in treatment of DAA-experienced Egyptian CHC genotype 4 patients (male sex, 52.2%; mean age, ± SD = 45.6 ± 9.7 years) [19].

Baseline values of liver transaminases as well as values at the end of treatment were insignificantly different between the study groups; however, both ALT (alanine aminotransferase) and AST (aspartate aminotransferase) levels significantly decreased in both groups at the end of treatment as compared to baseline values. This was in agreement with the findings of El Kassas et al., who reported that ALT levels in CHC patients significantly decreased after the end of treatment [20].

Baseline HCV RNA levels were insignificantly different between the two groups in the present study; the mean HCV RNA at baseline was $631.6 \times 10^3$ IU/mL and $787.8 \times 10^3$ IU/mL for group A and B, respectively ($p = 0.782$).

In the current study, SVR rates showed no significant difference between the two study groups; the SVR12 rate was 94.4% (51/54 patients) and in group A and 96% (48/50 patients) in group B ($p = 1.000$). These results are in agreement with those reported by Abdel-Moneim et al., who used a combination of SOF plus OBV/PTV/r + RBV in treatment of DAA-experienced Egyptian CHC genotype 4 patients. In that study, the overall SVR12 rate was 97% (109/113 patients). Of note, 95 out of the 113 patients (84%) were SOF/DCV experienced [19].

The SVR rates in the current study were also comparable to those reported by Bourlière et al. in the POLARIS-1 study. In that trial, the triple combination of SOF/VEL/VOX was used for 12 weeks to treat CHC patients after an unsuccessful NS5A-containing DAA regimen. The overall SVR rate was 96% (253/263) of treated patients, while SVR was 91% in patients with HCV genotype 4 (20/22 patients) [21].

The SVR rates observed in the present study were also comparable to those reported by Ledinghen et al., who used a combination of GLE/PIB or GLE/PIB plus SOF for retreatment of difficult-to-treat CHC patients who failed to respond to previous DAA-based regimens (including different NS5A inhibitors). In that study, SVR12 rates were 100% and 93.3% in the GLE/PIB plus SOF group and GLE/PIB group, respectively [22].

Also, Gane et al. achieved SVR rates comparable to those observed in the present study. In that study, the SVR rate was 91% (63/69 patients) when a combination of SOF/VEL + RBV was used for 24 weeks for retreatment of CHC patients who failed to respond after a regimen of SOF/VEL, SOF/VEL/RBV or SOF/VEL/VOX for different treatment durations (4-12 weeks) [23].

Hèzode et al., in a real-world study, used the SOF/SMV combination for 12 weeks to treat CHC patients who failed to respond to a previous DCV-based regimen. In that study, the SVR rate was 87.5% (14/16), which is slightly lower than in the current study, which could be due to the small number of patients (16 patients) and the inclusion of patients only with advanced fibrosis or cirrhosis at baseline. This difference may also be attributed to the omission of an NS5A inhibitor and RBV in the treatment regimen [24].

The SVR rates in the present study were higher than those reported by Lawitz et al., who evaluated the efficacy of SOF plus ledipasvir (LDV) for 24 weeks for retreatment of CHC genotype 1 patients who failed after 8 or 12 weeks of treatment with SOF/LDV ± RBV (SVR = 73%, 30/41 patients). This difference between the studies was probably due to a difference in the HCV genotype and/or the omission of a protease inhibitor and RBV in the regimen used in that trial [25].

Regarding safety and tolerability, both regimens used in the present study were generally safe and well tolerated, with no deaths due to AEs. Among all of the study patients, only one patient in group B discontinued treatment after 4 weeks due to hepatic decompensation in the form of significant elevation of total bilirubin (6.4 mg/dl) and development of ascites. Surprisingly, this patient achieved SVR12.

Reported AEs in the current study were generally mild to moderate (grade 1 or 2 severity) in both study groups; however, dermatological AEs were significantly more common among group B patients, while headache was significantly more common in group A [18].

In the group A patients, the most commonly reported AEs were fatigue (29.6%), headache (20.4%), abdominal pain (18.5%) and musculoskeletal pain (14.8%), which were similar to AEs reported by Abdel-Moneim et al. in patients who received a combination of SOF plus OBV/PTV/r + RBV. The most common AEs observed in that study were headache (22%), fatigue (20%), asthenia (18%), dyspnea (17%), nausea (14%), and abdominal troubles (13%) [19].

In group B patients, the most commonly reported AEs were fatigue (28%), photosensitivity (14%), itching (14%), and abdominal pain (10%). AEs observed in the current study share some similarity with those reported by Sulkowski and colleagues. In that trial, a combination of SOF/SMV/DCV for 6 or 8 weeks was used to treat naïve patients with CHC genotype 1. AEs reported in that trial were grade 1 or 2 except for one patient who had serious

AE. The most common AEs reported were headache (23.5%), fatigue (22.1%), nausea (14.7%), and diarrhoea (8.8%). The incidence of skin and subcutaneous tissue disorders was low in that study (pruritus, 4.4%; alopecia, 2.9%; photosensitivity, 2.9%; rash, 1.5%; skin exfoliation, 1.5%), which was different from the current study, probably due to differences in genetics, ethnicity, race, or degree of exposure to sunlight between the patients in the two studies [26].

The most common AEs observed in patients who received the SOF/VEL/VOX regimen in the POLARIS-1 study were headache (in 25% of patients), fatigue (21%), diarrhea (18%), and nausea (14%) [21].

Regarding laboratory abnormalities observed in the present study, a clinically significant drop in hemoglobin levels was observed in both study groups; however, there was no statistically significant difference between the groups (33.3% and 44% in group A and B, respectively). Hemoglobin drops were mostly of grade 1 or 2 severity, except for one patient in group A who suffered a severe drop (grade 3) in hemoglobin (7.0 g/dl) that might have been induced by ribavirin [18].

Clinically significant hyperbilirubinemia was observed in both groups during treatment. In addition, significantly higher total bilirubin levels were observed in group B than in group A at week 4 of treatment. The amount of elevation in total bilirubin in the study patients were generally mild to moderate (grade 1 or 2), with the exception of two 2 patients, one in each group, who suffered severe (grade 3) hyperbilirubinemia (4.2 and 6.4 mg/dl) [18].

Changes in serum creatinine in both study groups were statistically significant only at week 8 of treatment, when it was significantly higher in group A. However, these changes were clinically insignificant. In addition, there were no statistically or clinically important changes observed in platelet count, white blood cell count, or AFP levels between the groups in the present study.

The main limitation of this study may be the relatively small sample size. Further research on a larger scale with more patients is therefore necessary.

## Conclusions

Reliance on SOF as a backbone of therapy in combination with two other DAAs targeting different viral proteins is an efficient strategy for retreatment of CHC after failure of NS5A inhibitor-based regimens. The combination of SOF plus OBV/PTV/r ± RBV or SOF/SMV/DCV ± RBV represents a lifeline for retreatment of Egyptian CHC patients who fail to respond to SOF/DCV-based therapy, especially in a setting where DAAs availability is limited.

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## Compliance with ethical standards

**Conflict of interest** :The authors declare that there is no conflict of interest.

**Informed consent** Participants provided written informed consent, and the study was approved by the institutional ethical committee.

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