Original Article

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The outcome of combined treatment with ombitasvir-paritaprevir-ritonavir, sofosbuvir with or without ribavirin as salvage therapy for Egyptian HCV experienced patients: A single center study

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Summary **We aimed to investigate the efficacy and safety of combination of sofosbuvir with ombitasvir, paritaprevir, and ritonavir ± ribavirin as a retreatment option for experienced Egyptian patients who failed previous sofosbuvir, daclatasvir ± ribavirin therapy. A total of 75 treatment-experienced patients were allocated for the completion of their treatment period according to criteria formed by the national committee for control of viral hepatitis. The enrolled patients were followed up throughout treatment, at the end of treatment and 3 months after the end of the treatment by clinical evaluation and laboratory investigations. 27 patients were treated with sofosbuvir with ombitasvir, paritaprevir, and ritonavir plus ribavirin for 12 weeks while 48 patients were treated with sofosbuvir with ombitasvir, paritaprevir, and ritonavir without ribavirin for 24 weeks. The per-protocol sustained virological response at week 12 (SVR12) rate was 100% in both groups while the intention-to-treat SVR12 was 93.4% in all patients, 97.9% in the 24 weeks group and 85.2% in the 12 weeks group. The regimen was well tolerated and the most common adverse effects observed across treatment and during follow-up period included fatigue (38.6%) and headache (29.3%), withdrawal due to adverse effects occurred in 6.6%. We can conclude that retreatment with sofosbuvir with ombitasvir, paritaprevir, and ritonavir ± ribavirin is well tolerated and achieved high SVR12 rates in chronic HCV Egyptian patients with previous sofosbuvir plus daclatasvir treatment failure. Ribavirin free regimen for 24 weeks exerted significant lesser adverse effects.**

Keywords: Hepatitis C, salvage therapy, Egypt

1. Introduction

HCV is near to be epidemic in Egypt. Seroprevalence has been reported in about 8 million individuals (10% of Egyptians). Estimated 7-10% of Egyptian populations are chronically infected (*1-3*). Genotype 4 (GT4) infection accounts for 13-20% of HCV infections worldwide; in Egypt, it is present in about 93% of chronic HCV patients (*4*).

With the emergence of many HCV direct-acting antiviral therapy options, the Egyptian National Committee for Control of Viral Hepatitis (NCCVH) began to recruit HCV patients for treatment in September 2014 (*5*). According to the AASLD guidelines, the recommendations for treatment were sofosbuvir/daclatasvir (SOF/DCV) for 24 weeks without ribavirin (RBV) or 12 weeks with weight-based ribavirin (*6*). This regimen was associated with high rates of sustained virological response among "difficult to cure" patients (*7*).

In November 2015, generic SOF/DCV (± RBV) became the main treatment option for chronic HCV in the national program in Egypt. This therapy was evaluated later on in an Egyptian study included 18378 patients, SVR12 was achieved in 95.4% in SOF/DCV group and in 94.7% in SOF/DCV/RBV group. Relapse and nonresponder rates were 3.7% and 3.3% in both groups respectively (*8*).

SOF is a potent pan-genotypic NS5B polymerase inhibitor with a high barrier to resistance (*9*). Ombitasvir

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is an NS5A protein inhibitor and paritaprevir is an NS3/4A protease inhibitor are co-dosed with ritonavir (r) to increase drug exposures (*10*). These drugs are given in combination to increase their efficacy and prevent HCV resistance-associated substitutions (*11*). The most favorable plan for retreatment of HCV experienced patients with previous direct-acting antivirals (DAAs) failure is sofosbuvir plus other class drugs not previously used and ribavirin unless it is contraindicated to consider triple or quadruple DAAs treatment (*12*).

Minimal data and clinical trials for retreatment in Egyptian patients with HCV GT4 who failed prior DAAs treatments are present as most of the studies focused on the treatment of patients with genotype 1 infection which has the highest worldwide prevalence (*13*), therefore, this study was conducted for evaluation of the efficacy and safety of the combination of quadruple DAAs; SOF/ombitasvir/paritaprevir/ritonavir/±RBV as salvage therapy for retreatment of experienced Egyptian patients who failed previous treatment with SOF/DCV therapy.

2. Patients and Methods

2.1. *Patients*

This study included a total of 75 experienced patients with chronic hepatitis C and all stages of liver fibrosis (F0-F4) indicated for treatment according to inclusion and exclusion criteria who failed to achieve SVR12 following previous treatment with sofosbuvir and daclatasvir regimens.

All patients were recruited from Faqous general hospital specialized center affiliated to the NCCVH in Egypt, Sharkia governorate, Egypt in the period from Jan 2017 to April 2018. The study was conducted in accordance with the ethical standards of the responsible committee on human experiment (institutional and national) and with the Declaration of Helsinki. An informed consent was written by all patients before starting treatment to allow the use of their clinical data and for publication.

Inclusion criteria for treatment according to the supreme council and the national committee for control of viral hepatitis (NCCVH), December 2016: males and females ≥ 18 years; detectable HCV viremia by PCR; HbA1C < 9 % for diabetic patients; alpha-fetoprotein (AFP) < 100 ng/mL (Triphasic CT was ordered for exclusion of HCC if AFP > 100 ng/mL); female patients practicing contraception; wife of a male patient practicing contraception; patients older than 65 years old should undergo cardiac evaluation by ECG, echocardiography and cardiac consultation before treatment; noncirrhotic and compensated cirrhosis (Child's class A) who failed previous treatment with sofosbuvir and daclatasvir (easy to treat group) or sofosbuvir, daclatasvir and ribavirin (difficult to treat group).

Exclusion criteria for treatment according to the supreme council and the national committee for control of viral hepatitis (NCCVH), December 2016: patients with Child's class B and C; patients with hepatocellular carcinoma except after 6 months of successful radical curative intervention aiming at a cure with no activity as detected with dynamic imaging as CT or MRI; apregnant female or inability to implement effective contraception; inadequate control of diabetes (HA1C % > 9); extrahepatic malignancy excepts after 2 years of a disease-free interval; patients with hypersensitivity to drugs.

2.2. *Methods*

All subjects underwent thorough history taking (including a history of hepatic encephalopathy, ascites, previous HCV treatment, adherence to previous treatment, previous endoscopies or upper GIT bleeding, diabetes, hypertension, smoking, and contraceptive pills usage or other drug histories) and through physical examination.

2.3. *Routine Biochemical measurements*

Serum total and direct bilirubin, albumin, serum alanine transaminase (ALT) level, aspartate transaminase (AST), urea, creatinine, CBC, prothrombin time (PT), prothrombin concentration, partial thromboplastin time (PTT), International Normalizing Ratio (INR), fasting, postprandial blood sugar, HA1c, AFP, HBs antigen, pregnancy test, and PCR for HCV-RNA (the lower limit of detection of HCV-RNA was 12 IU/ML).

2.4. *Radiological investigations*

Pelvi-abdominal ultrasonography for examination of the liver, portal vein diameter, spleen, detection of hilar varices, focal lesions and ascites.

2.5. *Staging of liver fibrosis*

Was assessed by Metavir Score (if available), FIB-4 or Transient elastography scoring (Fibro scan if available) at any time prior to enrolment. Cirrhosis was diagnosed when patients show cirrhosis in their liver biopsy, liver stiffness by Fibroscan of 12.5 kPa or more or Fib-4 > 2.5.

2.6. *Treatment protocols*

Generic SOF was supplied to the Ministry of Health centers by many manufacturing Egyptian facilities as AUG Pharma, Marcyrl, and Pharco while generic ribavirin was supplied by Amriya pharmaceutical, Egypharma, Mash Pharmaceuticals, Pharco, and T3A pharmaceuticals. Ombitasvir, paritaprevir, ritonavir was supplied as Qurevo® by Abbvie pharmaceuticals.

SOF/OBV/PTV/r + RBV group (ribavirin eligible

subjects): received treatment for 12 weeks: Sofosbuvir 400 mg once daily; ombitasvir 25 mg + paritaprevir 150 mg and ritonavir100mg (two capsules) PO q Day with the meal; Ribavirin (RBV) was supplied in 200 mg capsule, recommended dose: 1,200 mg daily if weight > 75 kg or 1,000 mg daily if weight ≤ 75kg divided daily dose BID with food.

SOF/OBV/PTV/r group (ribavirin ineligible subjects): received treatment for 24weeks: Sofosbuvir 400mg once daily; ombitasvir25mg + paritaprevir 150 mg and ritonavir100mg (two capsules) PO q Day with the meal.

RBV ineligible/intolerance was defined as: Neutrophils < 750 cells/mm^3, results within the past protocol therapy; Haemoglobin < 10g/dL, results within the past protocol therapy; Platelets < 50,000 cells/mm^3, results within the past protocol therapy; Autoimmune hepatitis or other autoimmune condition is known to be exacerbated by ribavirin; Known hypersensitivity to ribavirin within the past protocol therapy.

Monitoring of treatment and adverse effects was done by: Quantitative PCR 12 weeks after the end of the treatment protocol to confirm viral eradication and detect SVR12; ALT, AST every month; Bilirubin (total and direct) and CBC every 2 weeks in patients subjected to 12 weeks therapy and every month in patients subjected to 24 weeks therapy. Ribavirin dose was reassessed according to hemoglobin level and ministry of health (MOH) protocol. Discontinuation of treatment was planned on the experience of severe adverse effects as severe anemia, jaundice or new liver decompensation.

2.7. *Endpoints*

The primary endpoint represents a sustained virological response (HCV RNA < 12 IU/mL), observed 12 weeks after the end of the treatment (SVR12).

2.8. *Statistical analysis*

The obtained data were analyzed statistically using SPSS program version 20 (SPSS, Chicago, IL). Data were expressed as means ± standard deviation in quantitative variables; and numbers and percentages for qualitative variables. T-Test for variables with normal distribution, Mann-Whitney *U* test for variables with abnormal distribution, Chi-Square tests (χ^2) were used when appropriate. The results were considered statistically significant if the *p* value was < 0.05.

3. Results

3.1. *Basic characteristics and demographic data of studied patients*

Ribavirin eligible treatment-experienced patients (*27*) were treated with SOF with OBV/PTV/r plus RBV for 12 weeks while ribavirin ineligible treatment-experienced patients (*48*) were treated with SOF with OBV/PTV/r for 24 weeks.

The two groups of treatment were matched regarding age, sex, comorbid factors as diabetes, hypertension, and smoking. A significant difference between the two groups was found as regards total bilirubin, INR, and FIB4 score, as well as the number of cirrhotic patients, being higher in SOF with OBV/PTV/r group that were ribavirin intolerant. Also, albumin, WBC's count, hemoglobin concentration, and platelets count were significantly lower. However, no significant difference as regards other variables were found ($p > 0.05$) (Table 1).

3.2. *SVR rates*

Per-protocol SVR rates were 100% with no treatment failure in both investigated groups while the intention-to-treat results were 93.4% in all patients, 97.9% in SOF with OBV/PTV/r group and 85.2% in SOF with OBV/PTV/r + RBV group (Figure 1 and 2).

3.3. *Adverse effects and discontinuations*

The regimen was generally well tolerated and the most common adverse effects observed across treatment and during the follow-up period included fatigue (38.6%), headache (29.3%), and hyperbilirubinemia (21.3%) (Table 2). These adverse effects were slightly significantly more notable in the ribavirin group ($p < 0.05$).

Current study data revealed there were no deaths, but discontinuations of therapy recorded due to adverse effects as severe jaundice and pruritis occurred in five patients (6.6%) that was slightly more significant in SOF with OBV/PTV/r + RBV group ($p < 0.05$) (Figure 2, Table 2).

4. Discussion

Treatment of HCV with the new era of DAAs offered a renewed hope to Egyptian patients. According to NCCVH treatment protocol (December 2016), the first option was combining 400 mg sofosbuvir and 60 mg daclatasvir in two separate tablets that was introduced in November 2015 and it was the most prevalent treatment option used due to the availability of low price local generics. The second option was treatment with the fixed-dose combination of ombitasvir, paritaprevir and ritonavir in two tablets given daily with food and weight-based ribavirin and was approved for use in Egypt in October 2015, however, this option was restricted to patients with renal failure.

Retreatment of HCV with DAA of the same class plus an addition of DAA with another mechanism of action and/or new DAA can achieve high SVR in patients that had previous treatment failure with DAAs treatments (*14*) for this reason combination therapy of

Table1. Basic characteristics and demographic data of studied patients

Items	SOF/OBV/PTV/r, (*n* = 48, 24 Weeks)	SOF/OBV/PTV/r + RBV, (*n* = 27, 12 Weeks)	*p*-value
Age (y) (M ± SD)	52.6 ± 9.02	48.2 ± 10.6	0.66
Male	35 (72.9%)	18 (66.6%)	0.56
Female	13 (27.1%)	9 (33.4%)	
Diabetes	6 (12.5%)	3 (11%)	0.85
Hypertension	5 (10.4%)	4 (14.8%)	0.57
Smoking	9 (18.7%)	5(18.5%)	0.98
Laboratory data (M ± SD)			
Total bilirubin (mg/dL)	1.2 ± 0.31	0.81 ± 0.21	< 0.001*
ALT (ULN:40U/L)	63.3 ± 53.8	62.1 ± 31.4	0.91
AST (ULN:40U/L)	58.5 ± 30.8	56.4 ± 23.3	0.75
Albumin (g/dL)	3.6 ± 0.45	3.8 ± 0.17	0.03*
INR	1.4 ± 0.4	0.9 ± 0.5	< 0.001*
WBC ($\times 10^3/mm^3$)	5.3 ± 1.5	6.3 ± 1.2	0.004*
Haemoglobin (g/dL)	11 ± 0.86	12 ± 1.15	< 0.001*
Platelets ($\times 10^3/mm^3$)	120.6 ± 22.6	142.8 ± 22.06	< 0.001*
HCV PCR (IU/mL)	690234.36 ± 1803147.07	515033.27 ± 1337072.7	0.66
Type of patient			
Non cirrhotic	10 (20.8%)	12 (44.4%)	0.03*
Cirrhotic	38 (79.2%)	15 (55.6%)	
Previous treatment			
[a]SOF/DCV	3 (6.25%)	0 (0%)	0.64
[b]SOF/DCV/RBV	45 (93.75%)	27 (100%)	
FIB4	3.21 ± 0.9	2.42 ± 1	0.001*

*Significant value, [a]sofosbuvir/daclatasvir, [b]sofosbuvir/daclatasvir/ribavirin, ALT: alanine transaminase; AST: aspartate transaminase; INR: international normalized ratio; WBC: white blood cell count.

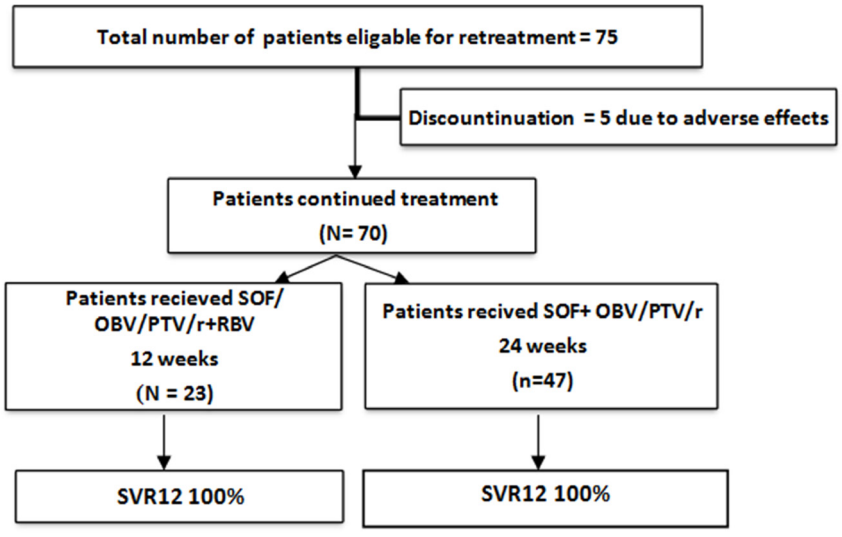

Figure 1. Per protocol SVR12 among patients completed the study.

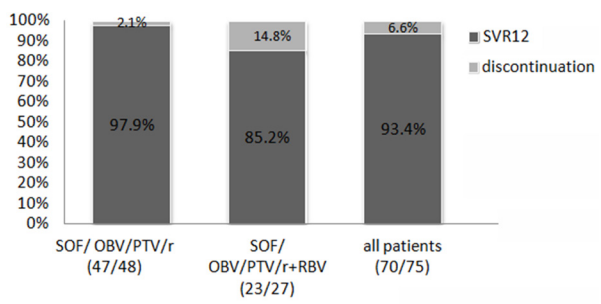

Figure 2. Intention to treat SVR12 and discontinuation percentages among treatment groups.

ombitasvir, paritaprevir, and ritonavir plus sofosbuvir was used and was the only treatment option available in Egypt for experienced patients who failed previous treatment with SOF/DCV therapy.

Optimizing treatment outcomes in patients with cirrhosis includes either the addition of RBV or prolonging treatment duration (*15,16*) for this reason, 48 patients in our study who were ribavirin ineligible were subjected to prolonged treatment period for 24 weeks.

Current study results showed that the per-protocol SVR12 rate was (100%; 70/70) in both studied groups

Table 2. Adverse effects among treatment groups

Items	SOF/OBV/P/r		SOF/OBV/PTV/r+ RBV		Total		*p*-value
	No	%	No	%	No	%	
Hyperbilirubinemia	6	12.5	10	37	16	21.3	0.01*
Diarrhea	5	10.4	7	25.9	12	16	0.78
Headache	10	20.8	12	44.4	22	29.3	0.03*
Itching/Rash/pruritus	5	10.4	8	29.6%	13	17.3	0.03*
Loss of appetite	8	16.6	6	22	14	18.6	0.55
Nausea	3	6.25	4	14.8	7	9.3	0.22
Insomnia	5	10.4	4	14.8	9	12	0.57
Fatigue	14	29.1	15	55.5	29	38.6	0.02*
Anaemia	1	2	5	18.5	6	8	0.01*

*Significant value.

without treatment failure while the intention-to-treat were (93.4%; 70/75) in all patients, (97.9%; 47/48) in SOF with OBV/PTV/r group, and (85.2%; 23/27) in SOF with OBV/PTV/r plus RBV group, near results obtained by Abdel-Moneim *et al*. (17) who evaluated retreatment efficacy of SOF/OBV/PTV/r + RBV for 12 weeks in HCV genotype 4 experienced patients who failed treatment with DAAs-based regimens and found overall per-protocol SVR12 rate (97%; 109/113), SVR12 was achieved by (98%; 81/83) of non-cirrhotic patients and (93%; 28/30) of cirrhotic patients. The SVR12 results differences between the current study and Abdel-Moneim *et al*. may be due to more limited number of cases in the current study. However, in the current study similar SVR12 for both cirrhotic and noncirrhotic patients who completed treatment protocol duration was found.

Sanai *et al*. (*18*) assessed the efficacy of co-formulated ombitasvir/paritaprevir/ritonavir in the treatment of HCV GT4 ± RBV with chronic kidney disease stage 4-5. This study included treatment-naïve and peginterferon/RBV-experienced GT4-infected patients (n = 32) treated for 12-24 weeks, 19.4% were treated without RBV; Overall, 97.1% patients achieved SVR12, including 100% of those with a post-treatment follow-up (modified ITT analysis) with no virological failures. The virological response was equal in both treatment naive and experienced, cirrhotic and noncirrhotic and those who received or not received ribavirin.

Despite the recommendation for the addition of RBV in the product label and in guidelines, 48 patients who were ribavirin ineligible were treated without RBV for 24 weeks. All patients who received a RBV-free regimen achieved SVR12, however, they recommended that the role of RBV must be further explored in larger clinical trials. Our study shows that RBV-free cohort (24 weeks) achieved high SVR12 with less significant side effects than RBV-containing one (12 weeks).

According to current results, neither baseline demographic features as age and sex nor comorbid factors as DM, hypertension, and smoking affected SVR12. In addition, the virological response was unaffected by the degree of viremia, previous treatment protocols nor fibrosis degree assessed by FIB4 results, a similar conclusion was reached by other studies who confirmed that age, body mass index, HCV-RNA levels, GT4 subtype, and IL-28B genotype, may not impact significantly on the virological response (*17,18*).

The regimen was generally well tolerated and the most common adverse effects observed across treatment and after follow-up were fatigue and headache. Our findings were in agreement with the studies of Abdel-Moneim *et al*. (*17*) and Sanai *et al*. (*18*).

Hyperbilirubinemia is the most observed laboratory abnormality and was responsible for discontinuations of therapy in five patients due to severe jaundice and pruritis, this may be explained by ribavirin-induced hemolysis and known inhibition of the organic anion transporting polypeptide 1B1 bilirubin transporter by protease inhibitors (*19*).

In conclusion, the combination of sofosbuvir with ombitasvir, paritaprevir, ritonavir ± RBV is well tolerated and achieved high SVR12 rates in chronic HCV GT4 Egyptian patients with previous SOF/DCV treatment failure. Ribavirin free regimen for 24 weeks had high SVR12 as 12 weeks ribavirin regimen with lesser adverse effects and offered a hope for treatment of patients who are ribavirin intolerant.

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