

Research Article

Sofosbuvi, Daclatasvir, Simeprevir and Ribavirin as a Re-Treatment Approach in HCV Patients Genotype 4, Egyptian Study

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Abstract

Background: Chronic HCV in whom prior DAA treatment had failed, outcomes after retreatment are optimal. Combination of SOF, DCV, SIM, and Ribavirin in treatment experienced patients, as recommended in current guidelines despite scarce data.

Aim: To determine the efficacy and safety of SOF, DCV, SIM plus RBV in Egyptian patients infected with chronic HCV GT4 who failed prior DAAs treatments.

Methods: One hundred and seventeen patients failed to respond to SOF containing regimens were randomized according to previous response to therapy to non-responders and relapses. Duration of therapy (12 weeks and 24 weeks) according to fibrosis stages. SOF, DCV, SIM and weight based RBV 12 weeks for f1 and f2 (group I) and 24 weeks for f3 and f4 (group II).

Results: In the non responders SVR were 100%, in group I (f1 & f2) and 97% in group II (f3 & f4). Relapse was 3% in group II (f3 & f4). No patients from either two groups had breakthrough or non response. In relapsers SVR were 100%, in group I (f1 & f2) group an 96% in group II (f3 & f4) .Breakthrough, relapse and non-response were 2%, 4%, 2% respectively only in group II (f3 & f4).

Conclusion: Careful choice of combining multiple DAAs with different viral targets and non-overlapping resistance may be an effective treatment strategy in difficult-to-cure patients, and allow for shorter durations of treatment.

Keywords: HCV; Simeprevir; Sofosbuvir; Daclatasvir; SVR

Abbreviations

SIM: Simeprevir; SOF: Sofosbuvir; DCV: Daclatasvir; RBV: Ribavirin; F: Fibrosis; SVR: Sustained Virologic Response; HCV: Hepatitis C Virus; RVR: Rapid Virological Response; EOTR: End of Treatment Response; DAAs: Direct Antiviral Agents

Introduction

However, rare clinical trials were reported on the regimen, Sofosbuvir (SOF) with Daclatasvir (DCV), simeprevir (SIM) (an HCV-protease inhibitor) plus RBV for retreatment of patients with HCV GT4 infection. Current data for patients with relapse after a DAAs containing regimen are limited, and supportive evidence is lacking. European Association for Study of Liver (EASL) recommendations in 2016 advise that retreatment be based on an interferon-free combination, including Sofosbuvir as a backbone (because of its higher barrier to resistance), with no cross-resistance with the previously administered drugs, with 1 to 3 other DAAs plus ribavirin for 12 to 24 weeks (24 weeks in patients with an f3 or f4 METAVIR

fibrosis score). We perform a prospective, real world study to evaluate the efficacy and safety of SOF, DVC, and SIM with Ribavirin in chronically infected patients whose prior treatment failed.

Methods

Study design

The study design is illustrated in Figure 1. The present cohort includes 117 treatment patients failed to respond to SOF containing regimens as proved by persistent viremia (Figure 2). Study subjects were randomized according to previous response to therapy to non-responders and relapsers.

The relapses (75 patients), who had an end-of-treatment response at the end of their first treatment but relapsed subsequently after the

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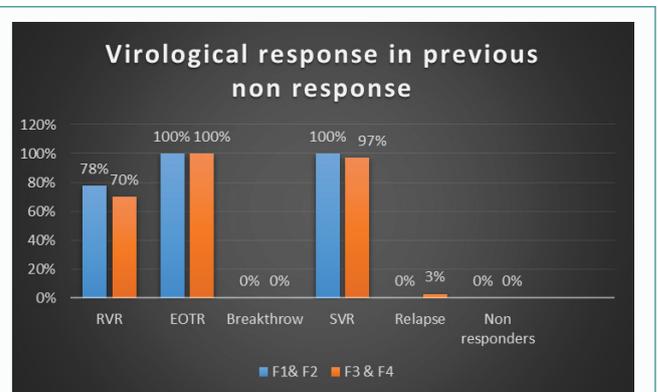
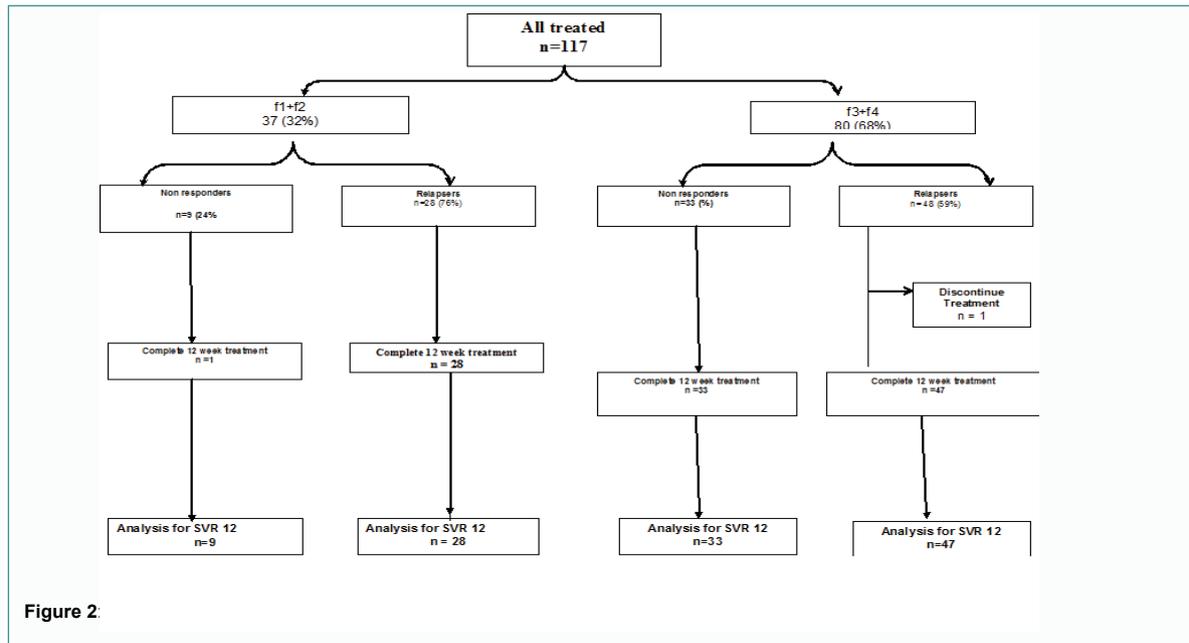


Figure 1: Response rates of patients with previous non response. RVR: Rapid Virological Response; EOT: End of Therapy response; SVR: Sustained Virological Response. Results were calculated based on per protocol analysis.



cessation of therapy, the non responders (42 patients), who did not achieve an end-of-treatment response at the end of the first treatment, including patients who had a breakthrough during treatment after an initial response.

Subsequent stratification according to duration of therapy (12 weeks and 24 weeks) was done according to fibrosis stages. SOF, DCV, SIM and weight based RBV 12 weeks for f1 and f2 or 24 months for f3 and f4. Our protocol was put in place according to EASL recommendations on treatment of hepatitis C, 2016 [1].

Treatment was with SIM 150 mg once a day, DCV 60 mg once a day, SOF 400 mg once a day and weight based RBV for 12 weeks in Patients with f1 and f2, and for 24 weeks in patients with f3 and f4, SOF dose was adjusted in patients whom their GFR reduced below 30 ml/min. Fibrosis status was assessed using transient elastography. Written informed consent was obtained from every participant (for both participation in the study and publication of the data). The institutional review boards approved this study.

Clinical, laboratory and virological follow up were done at a monthly interval throughout the treatment period and 3 months after end of treatment.

HCV genotyping

HCV genotyping done by direct sequencing of the 5' Untranslated Region (5'UTR), using RT-PCR-based assay (AmpliSens HCV-genotype-FRT PCR kit).

Efficacy end points

Treatment efficacy was assessed via measuring HCV RNA viremia at base line, at 4 weeks, end of therapy and 3 months after completion of treatment course. HCV RNA was measured using the Roche COBAS Taq Man HCV assay V.2.0.

Primary virological outcome was achievement of SVR12, defined as an undetectable HCV RNA 12 weeks after completion of HCV therapy.

Secondary virological outcomes included achievement of undetectable HCV RNA at 4 weeks of HCV therapy (Rapid Virological

Response (RVR) and End-of-Treatment Response (EOTR)), defined as undetectable HCV RNA at the completion or early discontinuation of HCV therapy.

HCV RNA levels were quantified with a lower limit of detection of 25 IU/mL at all sites.

Statistical analysis

Descriptive results are presented as means with standard deviations with inter quartile ranges for continuous data. Categorical variables were summarized by percentages. Comparisons of baseline variables between trial groups were performed with the use Fisher's exact test for categorical variables. P value <0.05 was considered significant.

Results

Study patients

One hundred and seventeen patients with chronic HCV failed to respond to SOF containing regimens as proved by persistent viraemia at the end of treatment (non-responders) or those who relapsed subsequently after the cessation of therapy (relapsers) were completed the study.

They were recruited and treated using SOF, DCV, SIM and RBV 12 weeks for f1 and f2 and 24 weeks for f3 and f4 according to EASL 2016 recommendations. Study subjects were randomized into two groups: group I, 37 (32%) patients (f1 & f2), will receive treatment for 12 weeks and group II 80 (68%) patients (f3 & f4), will receive treatment for 24 weeks.

The mean age of included patients ranged from 37 to 65 years with mean age of 45 years; 78% were males. According to liver stiffness measurement 32% patients had f1 & f2, and 68% patients had f3 & f4. Patients finished 12, 24 weeks treatment of DCV / SOF/ SIM/ RBV therapies and 12 weeks of follow up after the end of treatment.

The baseline demographic characteristics were balanced among the two groups (Table 1).

Efficacy in non responders

Outcomes were available for the 42 patients, undetectable

Table 1: Baseline Characteristics of studied patients.

Characteristic	Total n=117	f1+f2† n=37 (32%)	f3+f4‡ n= 80 (68%)
Age (years) [mean, range]	45 (32-65)	41 (32-60)	39 (44-65)
Sex			
Males	91 (78%)	19 (51%)	72 (90%)
Females	26 (22%)	18 (49%)	8 (10%)
BMI (kg/m ²)	27.8 ± 4.9	22.6 ± 3.6	21.1 ± 3.1
HCV RNA PCR	108.5 ± 42.7	110.3 ± 43.1	112.8 ± 39.3
Previous treatment regimens			
SOF+DCV	90 (77%)	25 (68%)	65 (81%)
SOF+LED	24 (21%)	12 (32%)	12 (15%)
SOF+SIM	3 (3%)	0 (0%)	3 (4%)
Previous treatment response			
Non responders	42 (36%)	9 (24%)	33 (41%)
Relapses	75 (64%)	28 (76%)	47 (59%)
Platelet count			
≥ 150 × 10 ⁹ /L	76 (65%)	28 (76%)	48 (60%)
≤ 150 × 10 ⁹ /L	41 (35%)	9 (24%)	32 (40%)
Elevated ALT	68 (58%)	19 (51%)	49 (61%)
Comorbid diseases			
Diabetes Mellitus	22 (19%)	15 (41%)	7 (9%)
Hypertension	11 (9%)	8 (22%)	3 (4%)
HCV related cryoglobinaemia	2 (2%)	2 (5.4%)	0 (0%)

Data are expressed as n (%); mean with range or standard deviation
 SOF: Sofosbuvir; DCV: Daclatasvir; LED: Ledipasvir; SIM: Simprevir
 †Liver stiffness was determined by Fibro scan: f1 to f2 (7 kpa to 9 kpa), f3 (9 kpa to 12 kpa), f4 (> 12.5 kpa)

viraemia after 4 weeks of treatment initiation (RVR) in previous non responders patients was 7/9 (78%), 23/33 (70%), respectively, using the per protocol analysis for both groups [group I (f1 & f2) and II (f3 & f4)] (Figure 1). EOTR and SVR % in group I (f1 & f2) and II (f3 & f4) were 9/9 (100%), 33/33 (100%), 9/9 (100%), 32/33 (97 respectively, relapse was 1/33 (3%) in group II (f3 & f4) only. No patients from either two groups had breakthrough or non response (Figure 1).

Efficacy in relapsers

Regarding to patients with previous relapse, RVR was 23/28 (86%), 38/47(80%) using per protocol analysis for both groups [group I (f1 & f2) and II (f3 & f4)], EOTR and SVR in group I (f1 & f2) and II (f3 & f4) were; 28/28 (100%), 46/47 (98%), 28/28 (100%), 45/47 (96%), respectively. Breakthrough, relapse and non-response were 2%, 4%, 2% respectively only in group II (f3 & f4) (Figure 3).

Factors influencing the SVR rate are compared in Table 2. SVR rate patients were significantly high in younger age than elders only in non responders (P<0.05). The SVR rate in the relapsers and

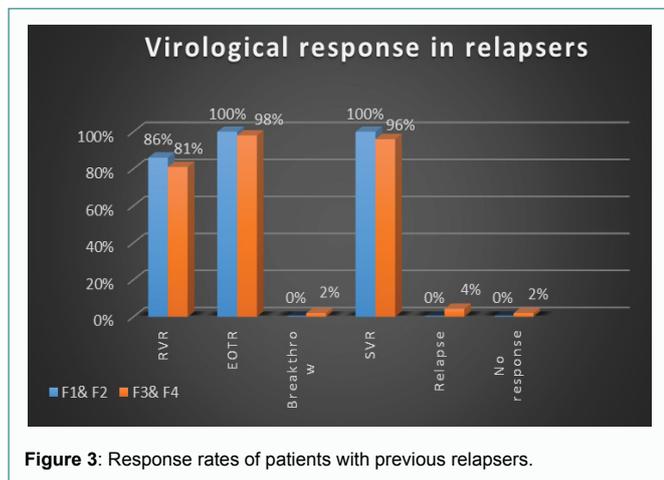


Figure 3: Response rates of patients with previous relapsers.

non-responders patients who achieved undetectable HCV RNA at week 4 was significantly higher than that in patients who achieved undetectable HCV RNA at week 12 (81% vs. 16%, P<0.005 & 71 % vs. 26% , P<0.002, respectively). Regarding to modification of RBV dose, The SVR rate patients with no dose modification was significantly higher than those with discontinuation of RBV (100% vs. 78%, P<0.003 & 100% vs. 80%, P<0.005, respectively). The SVR rates were significantly low in patients who stopped RBV than those who didn't modified or reduced the RBV. In contrast, there was no difference in the SVR rate in relation to, sex, Baseline HCV RNA and fibrosis stages in both relapsers and non responders (P<0.09, P<0.06 & P<0.08, P<0.07 & P<0.07, P<0.06, respectively).

Safety and tolerability

No serious side effects were recorded among the studied patients, about 80% of patients reported fatigue, anemia (18%), headache (12%), photosensitivity (3%), hyper bilirubinaemia (4%), pruritus (15%) and hepatic decompensation (0.8%), (Figure 4).

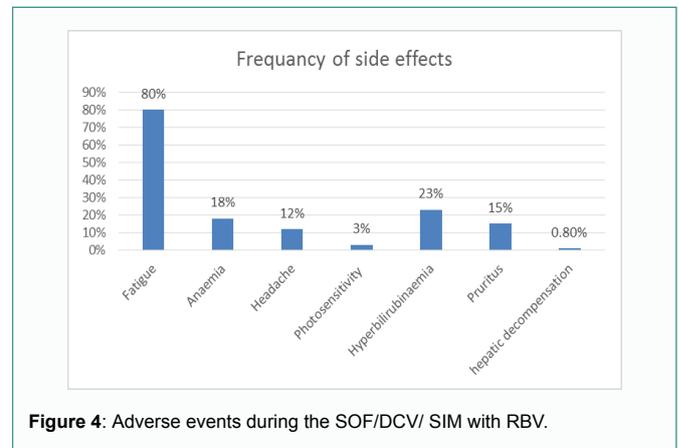


Figure 4: Adverse events during the SOF/DCV/ SIM with RBV.

Table 2: Comparison of factors influencing the SVR rate in treated patients.

	Relapsers (n=75)	Non-responders (n=42)
Gender		
Male (n=91)	61/63 (97%)	27/28 (96%)
Female (n=26)	12/12 (100%)	14/14 (100%)
P-value	<0.09	<0.06
Age		
30 to 50 y	48/49 (98%)	27/27 (100%)
50 to 70 y	25/26 (96%)	14/15 (93%)
P-value	<0.06	<0.05
Baseline HCV RNA (log10 IU/L)		
≤ 100,000 IU/ml	49/51 (96%)	19/19 (100%)
≥ 100,000 IU/ml	24/24 (100%)	22/23 (96%)
P-value	<0.08	<0.07
Fibrosis stages		
f1 to f2	28/28 (100%)	9/9 (100%)
f3 to f4	45/47 (96%)	32/33 (97%)
P-value	<0.07	<0.06
Undetectable HCV PCR		
4 week	61/75 (81%)	30/42 (71%)
24 week	12/75 (16%)	11/42 (26%)
P-value	<0.005	<0.002
RBV dose		
No dose modification	54/54 (100%)	31/31 (100%)
Reduction in RBV dose	12/12 (100%)	6/6 (100%)
Stop RBV	7/9 (78%)	4/5 (80%)
P-value	<0.003	<0.005

SVR: Sustained Virological Response; RVR: Rapid Virological Response; RBV: Ribavirin
 Data are expressed as n (%).

Discussion

However, rare clinical trials were reported on the regimen, SOF, DCV, SIM plus RBV for retreatment of patients with HCV GT4 infection. Thus, the present cohort study aimed to explore the efficacy and safety of SOF with DCV/SMV plus RBV in Egyptian patients infected with chronic HCV GT4 who failed response to SOF containing regimens as proved by persistent viraemia.

Treatment was with SIM 150 mg once a day, DCV 60 mg once a day, SOF 400 mg once a day and weight based RBV for 12 weeks in Patients with f1 and f2, and for 24 weeks in patients with f3 and f4.

In patients with HCV genotype 1 or 4 and those with f3 fibrosis or compensated cirrhosis, in whom treatment with an NS5A inhibitor has failed, EASL recommends retreatment with ribavirin plus either sofosbuvir, grazoprevir, and elbasvir or sofosbuvir, simeprevir, and daclatasvir for 24 weeks [1].

Current European recommendations for the retreatment of patients who have failed a regimen containing one or more second-wave DAAs are based on indirect evidence (HCV genotype, resistance profiles, the number of drugs administered, use of RBV, and treatment duration) and state "Intuitively, patients who failed on a DAA-containing regimen should be retreated with an IFN-free combination including a drug with a high barrier to resistance (currently, sofosbuvir), plus one or two other drugs, ideally with no cross-resistance with the drugs already administered. Based on results in difficult to-cure patient populations, retreatment should be for 12 weeks with ribavirin, or extended to 24 weeks with or without ribavirin [2].

This is the first time that the combination of simeprevir, sofosbuvir and daclatasvir (three unique DAAs with different mechanisms of action and non-overlapping resistance) has been assessed in HCV GT4-infected patients with different fibrosis grades.

The SVR rates for previous non responders and relapsers were 97% and 6%, respectively. Breakthrough, relapse and non-response occur in previous relapsers only In contrast to the non responders ,indicates that the HCV RNA response to previous treatment may be one of predictive factor for treatment failure.

Lawitz et al. [3] reported that treatment for 12 weeks with simeprevir, daclatasvir and sofosbuvir was generally safe and well tolerated, and resulted in 100% of cirrhotic patients with portal hypertension or decompensated liver disease, suggesting that the addition of a third DAA to the simeprevir/sofosbuvir regimen was beneficial in overcoming the limitations of the dual combination when treating patients with cirrhosis.

Also, Hézode et al. [4] reported that 60% of DAA experienced patients treated with a combination of SOF/DCV/ SMV plus RBV achieved SVR at 12 weeks. The study included a small group of 12 patients only.

In contrast to the previously described Phase II IMPACT study we did not include patients with decompensated liver diseases or portal hypertension in our study due to limited use of simeprevir in decompensated patients according to EASL 2016 guidelines.

The combination of simeprevir and sofosbuvir for 12 weeks without ribavirin was assessed in two Phase III trials in treatment-naïve and (peginterferon ± ribavirin) treatment-experienced HCV GT1-infected patients with (OPTIMIST-2) or without (OPTIMIST-1)

compensated cirrhosis [5,6]. The regimen demonstrated superiority in SVR12 rates over historical control data in both studies.

OPTIMIST-1, a phase III, randomized study reported that SIM/SOF for 12 weeks has less relapse rate than the 8-week treatment.

Another phase II open-label study (OSIRIS) conducted in Egypt .Non-cirrhotic patients were randomized to receive 8 or 12 weeks of treatment whereas compensated cirrhotic patients received a 12 week regimen. SVR12 was 92.1% with all patients treated for 12 weeks regardless of cirrhosis stage [7].

It is important to mention that retreatment with DAA of the same class plus an additional DAA with a different mechanism of action and/or new DAA could achieve high SVR in patients that had previous DAA treatment failure [8].

The patients who achieved RVR had a higher SVR rate in patients who had no RVR in both non responders and relapsing groups (81% vs. 99%, $P < 0.005$ and 71% vs. 100%, $P < 0.005$) respectively. The SVR rate for young patients was significantly higher than that for older one in non responders (100% vs. 93%, $P < 0.05$). There was no significant difference in other characteristics of the patients in both groups.

In case report recorded by R. Safadi et al. [9] retreatment with sofosbuvir in combination with simeprevir resulted in a rapid viral decline at Week 2 that resulted in undetectable HCV RNA at retreatment Week 4. The patient achieved a SVR at both post-retreatment Weeks 12 and 24.

Our analysis showed that SVR12 rate patients with no dose modification were significantly higher than those with discontinuation of RBV (100% vs. 78%, $P < 0.003$ & 100% vs. 80%, $P < 0.005$, respectively).

Consistent with other studies, addition of RBV to the regimen for 12 or 16 weeks increased SVR12 rates to 83% and 89%, respectively, in patients with advanced fibrosis or compensated cirrhosis [10].

Also Buti and Esteban concluded that for the experienced patients the most favorable strategy for other than that is previously used. Moreover, unless it is contraindicated, RBV should also be added to consider triple or quadruple DAA regimens [11].

Only the IMPACT study has evaluated a ribavirin-free version of the same regimen administered for 12 weeks in 40 treatment-naïve or treatment-experienced patients No discontinuation due to adverse events occurred, and a 100% SVR12 rate was achieved. The between-study differences can probably be explained by the fact that our patients had already experience a failed DAA-based regimen.

Concerning safety and tolerability, mild adverse effects were reported and generally were transient. There were no deaths recorded, and only one patient had hepatic decompensation although did not discontinue the treatment.

However in study done by HézodeC et al. [4] two patients had severe side effects and discontinuing treatment, they had advanced liver disease, low platelet counts, and portal hypertension. However, neither had a history of decompensation, and they did not have any indications for liver transplantation in contrast, mitochondrial toxicity has not been reported with DAAs, although asymptomatic increases in lipase activity, lactic acidosis and self-limited pancreatitis have been reported with sofosbuvir and simeprevir and with sofosbuvir and ribavirin, indicating that the severe episode of mitochondrial toxicity observed could be treatment related. In addition, although

the condition was diagnosed as mitochondrial toxicity at the time, we could not rule out protease inhibitor-induced hepatotoxicity [12].

Thus, the current combination regimen was well tolerated and achieved excellent SVR rates with minimal side effects. Therefore, the careful choice of combining multiple DAAs with different viral targets and non-overlapping resistance may be an effective treatment strategy in difficult-to-cure patients, and allow for shorter durations of treatment.

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