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Real life Egyptian experience of efficacy and safety of Simeprevir/Sofosbuvir therapy in 6211 chronic HCV genotype IV infected patients

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Abstract

Background & Aims: Major changes have emerged during the last few years in the therapy of chronic HCV. Several direct acting antiviral agents have been developed showing potent activity with higher rates of sustained virological response, even in difficult-to-treat patients. This study explores real life experience concerning efficacy, safety and possible predictors of response for the first cohort of Egyptian patients with chronic HCV genotype IV treated with Sofosbuvir/Simprevir combination therapy.

Methods: This real life study recruited the first (6211) chronic HCV genotype IV Egyptian patients, who received antiviral therapy in viral hepatitis specialized treatment centres affiliated to the National committee for control of viral hepatitis. All enrolled patients received 12 weeks course of daily combination of sofosbuvir (400 mg) and simeprevir (150 mg). Patients were closely monitored for treatment safety and efficacy.

Results: Overall sustained virological response 12 rate was 94.0% while the end of treatment response rate was 97.6%. sustained virological response 12 rates in easy and difficult-to-treat groups were 96% and 93% respectively. Univariate and multivariate logistic regression analysis revealed significant association of low albumin (<3.5), cirrhosis and Fib-4 score (>3.25) with treatment failure. Fatal adverse events occurred in 23/6211 cases (0.37%) due to liver cell failure adverse events or SAEs leading to treatment discontinuation occurred in 97 patients (1.6%).

Conclusion: Sofosbuvir/Simeprevir combination is an effective and well tolerated regimen for patients with chronic HCV genotype IV.

KEYWORDS
efficacy, HCV genotype IV, safety, Sofosbuvir/Simeprevir

Abbreviations: <LLOQ, less than lower limit of quantification; AASLD, American Association for the Study of Liver Diseases; AEs, adverse events; DAAs, direct acting antiviral agents; DCV, daclatasvir; ETR, end of treatment response; FDA, food and drug administration; NCCVH, National committee for control of viral hepatitis; SMV, simprevir; SOF, sofosbuvir; SVR, sustained virological response.

1 | INTRODUCTION

Egypt is known to be among the countries with highest Hepatitis C virus (HCV) prevalence.[1] Based on Egyptian demographic survey from

2008 to 2012, 14.7% of the Egyptian population carried HCV antibodies [2] and 9.8% had an active infection.[3] In 2010, Egypt had the highest age-standardized cirrhosis mortality rate (72.7 deaths per 100 000).[4]

More than 90% of Egyptian patients with HCV are infected with genotype IV virus.[5] The previous standard of care treatment with peginterferon/ribavirin for 48 wks has been limited by both eligibility and tolerability,[6] with response rates of 40%-69%.[7]

Major changes have emerged during the last few years in the therapy of patients with chronic HCV. Several direct acting antiviral agents (DAAs) have been developed showing potent activity with higher rates of sustained virological response (SVR), even in difficult-to-treat patients.[8]

After the establishment of the National Committee for the Control of Viral Hepatitis (NCCVH) in Egypt and development of a National Control Strategy for Treatment of Viral Hepatitis[9] and then with the start of mass treatment programme introducing the newly developed DAAs, Ministry of health in Egypt declared the decline of prevalence rates of HCV antibody in the population aged 15-59 years from a total of about 14% in 2008 to about 10% in 2015 and that of HCV RNA to be 7.0%, with an estimated 29% reduction in HCV RNA prevalence.[10]

Among these new drugs is Sofosbuvir, a nucleotide analogue, HCV NS5B polymerase inhibitor. It was the first approved DAA with excellent tolerability and favourable pharmacokinetic profile, limited potential for drug interactions, potent antiviral activity and high genetic barrier against all HCV genotypes,[8] Another Food and Drug Administration (FDA) approved DAA is Simeprevir, which is a second generation NS3/4A protease inhibitor. Simeprevir is active against genotypes 1, 2, 4, 5 and 6 with demonstrated favourable safety and efficacy profiles and limited drug-drug interactions.[11]

WHO guidelines published on screening, care and treatment of patients with chronic HCV genotype IV infection, with or without cirrhosis, strongly recommended Sofosbuvir/Simeprevir (SIM/SOF) combination with or without ribavirin therapy as an option.[12]

This study explores the Egyptian experience concerning efficacy, safety profiles and possible predictors of response for SIM/SOF combination therapy in the first cohort of Egyptian patients with chronic HCV genotype IV treated with this combination therapy.

Key points

- HCV genotype IV in Egypt
- Sofosbuvir/Simeprevir therapy.
- Real life multicentre experience.
- Efficacy and safety.

2 | PATIENTS AND METHODS

This real life study recruited the first cohort of chronic HCV genotype IV Egyptian patients, who received SIM/SOF antiviral therapy in viral hepatitis specialized treatment centres affiliated to the National committee for control of viral hepatitis (NCCVH) in Egypt.

The NCCVH was established in 2006 under supervision of Egyptian ministry of health. The committee started a mass treatment project for HCV in 2008 with pegylated interferon- ribavirin therapy, and introduced the newly developed DAAs in October 2014 with an aim to decrease HCV prevalence. Great efforts were exerted in terms of improving access to treatment centres (>45 affiliated units established) in which well-trained specialists in hepato-gastroenterology are responsible for patient's management. Reduction in the cost of therapy with about 90% its original of cost in terms of US dollars for each regimen was achieved by NCCVH negotiations. Patients were then treated free of charge and were sponsored by governmental support agencies.

SIM/SOF combination therapy started to be included among treatment regimens since May 2015. This study included patients whose data were available for outcomes, namely SVR12, treatment failure or discontinuation. These patients started treatment since May 2015 till January 2016 and their SVR12 data were available by June 2016. Patients were recruited from 28 centres affiliated to (NCCVH) distributed throughout Egypt, as following:

- Four centres in Cairo governorate (1387 patients).
- Three centres in Alexandria governorate (1047 patients).
- Twelve centres in Delta region (2674 patients).
- Six centres in Upper Egypt (801 patients).
- Three centres in Suez Canal region (302 patients).

They were recruited according to the following inclusion and exclusion criteria

2.1 | Inclusion criteria

Patients aged 18-75 years with HCV-related chronic liver disease diagnosed by detection of both anti-HCV antibodies and HCV RNA.

2.2 | Exclusion criteria

During mass treatment of HCV, authorities tried to make safety restrictions that may not be applicable in other settings like in individualized treatment in other clinics.

- Child B and C cirrhosis as defined by total serum Bilirubin ≥2 mg/dL, albumin ≤ 2.8 gm/dL, INR≥1.7, presence of ascites or encephalopathy.
- Platelet count <50 000 mm^3 as moderate to severe thrombocytopenia is a common finding in decompensated liver disease with portal hypertension. This cut-off was commonly used for dose modification and discontinuation during interferon and ribavirin based therapy.
- Hepatocellular carcinoma except 4 weeks after intervention aiming at cure with no evidence of activity by dynamic imaging (CT, MRI).
- Extra hepatic malignancy except after 2 years of disease free interval.
- Pregnancy or inability to use proper contraception.
- Inadequately controlled Diabetes mellitus (DM).

Being not a randomized controlled study for evaluation of the efficacy and safety of the medications involved, but rather an analysis and interpretation of clinical data obtained from a real life application of the programme of the national committee of control of viral hepatitis in Egypt aiming at evaluation of the treatment options implemented in the national programme, and as informed written consent was taken from all patients for the use of their clinical data in research studies without appearance of their personal identification data, and as the work was carried out in accordance with Helsinki declaration, and following the guidelines of the ethical approval committees in Egypt, ethical committee approval statement was not required for our study.

- All patients were subjected to:
- Full history taking, including history of other causes of chronic liver disease, or factors which are likely to affect the natural history or progression of liver disease as alcohol intake, drug history and history of DM, autoimmunity, or genetic diseases, and a thorough clinical examination was performed.
- The following laboratory investigations: Liver biochemical profile including total, direct Bilirubin, Aspartate transaminase (AST), Alanine transaminase (ALT), Albumin (ALB), International normalized ratio (INR). Also complete blood count (CBC), HBsAg, HCV-PCR quantitative, serum Creatinine, Alpha feto protein (AFP), and Fasting blood sugar (FBS), HbA1c if diabetic. Pregnancy test was done for female patients in childbearing period.
- Abdominal ultrasonography to detect echopattern of the liver (ultrasonographic features of cirrhosis), presence of signs of portal hypertension, and to exclude hepatocellular carcinoma or other comorbidities.
- For assessment of fibrosis; fibroscan was used whenever possible and in view of limited resources during this mass treatment and unavailability of fibroscan in every viral centre nationwide; FIB 4 was used as a noninvasive routine biochemical method to assess for fibrosis stages. FIB 4 score was calculated for patient as following[13]:
- (Age x AST)/(Platelets x square route ALT) with cut-off<1.45 excludes advanced fibrosis ≥F3and cut-off>3.25 confirm advanced fibrosis.
- Patients were then categorized into easy and difficult-to-treat groups to guide treatment plan nationwide, where easy to treat group included those who were noncirrhotic (by clinical & ultrasonographic examination), with Fib-4 <3.25, albumin >3.5, total serum Bilirubin <1.2 mg/dL, INR<1.2 and Platelet count >=150 000 mm^3, while difficult-to-treat group included those who were cirrhotic (by clinical & ultrasonographic examination) and/or varices, F3-F4 stages on Metavir score in liver biopsy, with Fib-4 >3.25, albumin ≤ 3.5, total serum Bilirubin >1.2 mg/dL, INR >1.2, and platelet count <150 000 mm^3.

2.3 | Treatment regimen

All eligible patients received 12 weeks course of combination of daily sofosbuvir (400 mg) and daily simeprevir (150 mg), based on EASL guidelines published the same year; 2015 which mentioned this combination as an option for treatment of genotype IV patients, with promising data based on results of the COSMOS trial in patients infected with genotype 1.[14]

The efficacy and toxicity of concurrent drugs given for comorbidities and potential drug-drug interactions were revised prior to initiation of therapy and whenever possible, an interacting co-medication stopped for the duration of HCV treatment or switched to an alternative drug with less interaction potentials.

2.4 | Monitoring of treatment safety and efficacy

Patients were followed up on weeks 2, 4, 8 and 12 (end of treatment), and 24 (to test for SVR12).

2.5 | Monitoring of treatment safety

- Patients receiving simeprevir were instructed to use sun protection creams and limiting sun exposure as mild to moderate rash and photosensitivity might occur.
- History taking for any adverse events, and patients were asked specifically about the commonly reported adverse effects as headache, nausea, insomnia, pruritus, rash and photosensitivity, etc.
- The efficacy and toxicity of concurrent medications given for comorbidities and potential drug-drug interactions were revised every visit and whenever possible, an interacting co-medication stopped for the duration of HCV treatment or switched to an alternative drug with less interaction potentials.
- Clinical examination was performed for rash, or any manifestations of hepatic decompensation (ascites, jaundice & encephalopathy) especially in the difficult-to-treat population
- Liver biochemical profile, complete blood count & creatinine were tested every visit.
- Ultrasound examination if ascites was suspected.

2.6 | Monitoring of treatment efficacy

- Quantitative HCV-PCR was assessed prior to treatment, on week 12 (end of treatment response [ETR]), and week 24 (sustained virologic response at week 12 post treatment SVR 12.
- Virologic response was considered when HCV RNA is less than lower limit of detection (<LLOQ) 15 IU at the ETR, and post treatment on week 12 (SVR12).
- Treatment failure was defined as:
- Viral nonresponse, that is, HCV RNA persistently above LLOQ at end of treatment
- Viral Relapse was defined as confirmed HCV RNA above LLOQ during the follow up period for those achieved HCV RNA <LLOQ at the end of treatment.
- Treatment discontinuation: discontinuation due to adverse events was considered treatment failure.

TABLE 1 Baseline data of this study population in relation to SVR

	SVR (n=5839)	Non-SVR (n=372)	Total (n=6211)	*P* value
Age[a] (years)	53.48 ± 9.49	54.67 ± 8.69	53.55 ± 9.45	.02
Gender[b]				
Males	3130 (53.6%)	223 (59.9%)	3353 (54.0%)	.02
Females	2709 (46.4%)	149 (40.1%)	2858 (46.0%)	
BMI[a]	29.97 ± 6.06	30.03 ± 5.76	29.97 ± 6.04	.86
Comorbidities[b]				
DM	829 (14.2%)	52 (14%)	881 (14.2%)	.49
HTN	297 (5.1%)	15 (4.0%)	312 (5.0%)	.04
Post HCC	18 (0.3%)	2 (0.5%)	20 (0.3%)	.03
Post liver transplantation	4 (0.10%)	0 (0%)	4 (0.10%)	.90
ANA positive	94 (1.9%)	7 (1.9%)	101 (1.6%)	.73
HBsAg positive	28 (0.5%)	0 (0%)	28 (0.5%)	.18
Positive HBV DNA	6 (1.6%)	1 (7.1%)	7 (0.1%)	.13
HCV Treatment history[b]				
IFN naive	5033 (86.2%)	323 (86.8%)	5356 (86.2%)	.73
IFN experienced	806 (13.8%)	49 (13.2%)	855 (13.8%)	
Laboratory data[a]				
HCV RNA (IU) log 10	5.67 ± 0.90	5.50 ± 0.89	5.65 ± 0.89	<.01
ALT (IU/L) (ULN: 40 IU/L)	58.48 ± 39.56	61.63 ± 40.61	58.67 ± 39.61	.13
AST (IU/L) (ULN: 40 IU/L)	66.22 ± 42.81	71.86 ± 43.67	66.56 ± 42.88	.01
AFP (IU/L) (ULN: 10 IU/L)	13.71 ± 37.12	18.57 ± 42.95	14.10 ± 37.52	.06
Albumin (g/dL)	3.95 ± 0 .68	3.73 ± 0.57	3.94 ± 0.67	<.01
Total Bilirubin (mg/dL)	0.05 ± 1.06	1.07 ± 0.57	1.05 ± 1.04	.64
Indirect Bilirubin (mg/dL)	0.58 ± 0.44	0.63 ± 0.26	0.59 ± 0.43	.29
WBC×10^3/mm^3	6.69 ± 7.65	5.99 ± 4.72	6.64 ± 7.51	.08
HG (G/L)	13.33 ± 1.95	13.12 ± 1.71	13.32 ± 1.94	.04
Platelets × 10^3/mm^3	159.49 ± 69.52	136.80 ± 60.92	158.12 ± 69.24	<.01
PC (%)	83.49 ± 13.84	80.00 ± 14.45	83.26 ± 13.91	<.01
INR	1.15 ± 0.22	1.19 ± 0.17	1.15 ± 0.21	<.01
Creatine (mg/dL)	0.85 ± 0.33	0.86 ± 0.38	0.85 ± 0.33	.45
Glucose (mg/dL)	103.01±28.32	100.13 ± 27.10	102.82 ± 28.25	.06
E-CrCl	111.32 ± 38.16	109.41 ± 43.86	111.21 ± 38.50	.61
TSH	1.86 ±1.30	1.90 ± 1.33	1.86 ± 1.31	.65
Ultrasound findings[b]				
Liver cirrhosis	2351 (40.3%)	205 (55.1%)	2556 (41.2%)	<.01
Splenomegaly	1216 (43.1%)	96 (46.4%)	1312 (21.1%)	.51
Hepatic focal lesion	45 (1.1%)	7 (2.4%)	52 (0.8%)	.04
Ascites	9 (0.2%)	0.0 (0.0%)	9 (0.1%)	.45
FIB4[a]	3.76 ± 3.26	4.69 ± 3.43	3.82 ± 3.28	<.01
Stiffness/Kps[a]	16.92 ± 12.17	19.94 ± 12.75	17.07 ± 12.21	.16
Varices in upper endoscopy[b]	360 (6.2%)	37 (9.9%)	397 (6.4%)	.01

ALT, Alanine transaminase; ULN, upper limit normal; AST, Aspartate transaminase; AFP, Alpha feto protein; WBC, white blood cells; HG, haemoglobin; PC, prothrombin concentration; INR, International normalized ratio; E-CrCl, estimated creatinine clearance; TSH, thyroid stimulating hormone.

[a]Data are given in mean and standard deviation.

[b]Data are given in number of cases (%).

TABLE 2 Univariate and multivariate logistic regression analysis for variables associated with treatment failure

	Univariate			Multivariate		
	OR	*P* value	95% CI	OR	*P* value	95% CI
Male gender	1.37	.01	1.1-1.7	1.37	.01	1.1-1.7
Difficult to treat	1.9	<.01	1.5-2.5	1.9	<.01	1.5-2.5
Viraemia >600 000 IU	0.76	.01	0.61-0.95	0.76	.02	0.61-0.95
Previous treatment failure	0.97	.86	0.70-1.33			

2.7 | Statistical analysis

All baseline data were presented and compared according to outcome of treatment. They were 2 groups; SVR and non-SVR (nonresponders, relapsers and discontinued pts). Comparison of quantitative data was assessed by *t* student test for comparison of two groups or ANOVA for the 3 groups of failure of treatment. Comparison of qualitative data was assessed by Chi-square test. Multivariate analysis in which the failure of outcome is the dependent variable was done with all available predictors. In all tests, *P* was considered significant if <.05.

3 | RESULTS

In this study, we explored the data of the first 6211 cohort of Egyptian patients who received SIM/SOF combination therapy for treatment of chronic HCV. Baseline characteristics revealed that 54.0% were males (3353 of 6211) and 5356 patients were treatment naive (86.2%). Other baseline data are shown in Table 1.

Sustained Virologic Response rate (SVR12) in this study population was 94% (5839/6211). Among nonresponders; 150 patients (2.4%) failed to achieve negative viraemia at end of treatment. 97 patients (1.6%) discontinued their treatment due to serious adverse events and 125 patients (2%) relapsed. SVR12 rate among difficult-to-treat group was 93% (3800/4089), while easy to treat group showed 96% SVR12 rate (2039 out of 2122) (*P*<.01).

In univariate analysis, advanced fibrosis, male gender, lower baseline albumin, platelet count and higher baseline INR and AST were significantly associated with treatment failure (Table 1). On multivariate logistic regression analysis, being among difficult-to-treat group (patients with cirrhotic evidence as cirrhotic echopattern by Ultrasound, and/or varices, F3-F4 stages on Metavir score, Fib 4 index >3.25), high viraemia and male gender were significantly associated with treatment failure (Table 2). While previous treatment failure was not a predictor of treatment response.

Higher Fib-4 and INR, lower haemoglobin, platelets and estimated creatinine clearance were significantly associated with discontinuation of treatment among failure groups. Characteristics of patient population who showed treatment failure are shown in Table 3.

Adverse events leading to treatment discontinuation occurred in 97 patients (1.6%), liver cell failure with resultant mortality occurred in 23 cases (0.37%) of those who have been treated. Other causes of discontinuation of treatment are shown in Table 4.

4 | DISCUSSION

This cohort real life study represents, to the best of our knowledge, the largest series of HCV genotype IV Egyptian patients treated with (SIM/SOF) combination therapy. SVR12 rate was 94.0% ETR rate was 97.6%.

These results were matching with the published results of Phase IIa *OSIRIS* clinical trial, at the Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) in November, 2015. The OSIRIS trial, investigated once daily (simeprevir) in combination with sofosbuvir in HCV genotype IV infected patients (n=63), with and without cirrhosis, and demonstrated SVR12 rates of up to 100% in patients treated for 12 weeks regardless of fibrosis stage and treatment history.[15] Our results are comparable to those of Willemse et al., 2016 whose cohort of 53 patients with genotype 4 HCV infection with advanced fibrosis and compensated cirrhosis achieved SVR12 rate of (92%) after 12 weeks' treatment with SOF/SIM combination with or without ribavirin.[16] El-khayat et al., 2016 also assessed SVR 12 for 583 Egyptian patients with HCV genotype 4 infection who received 12 weeks of SIM/SOF without ribavirin. Overall SVR12 rate in his study was (95.7%), and among cirrhotic patients (F4 on Metavir score) was 80.8%.[17]

The combination of SIM/SOF in our study showed higher rate of SVR12 (94%) compared to that found in RESTORE trial that evaluated efficacy/safety of Simprevir with peginterferon-α-2a/ribavirin (PR) in 107 patients with chronic HCV GT4 infection both naive and experienced, and found an overall SVR12 of 65.4%.[18]

Our results were also higher than those achieved by Hezode and colleagues, in *2015* who studied the efficacy of daclatasvir-based therapy on 82 treatment-naïve patients with HCV genotype IV, The SVR rate was 78%, without a clear benefit in the absence of cirrhosis and the presence of CC-IL28B.[4] In addition, the effectiveness of the use of daclatasvir in combination with other oral therapies such as beclabuvir (75 mg or 150 mg) and asunaprevir for 12 weeks in treatment-naïve, noncirrhotic patients with HCV genotype 4 was evaluated in a pilot study (n=21), and revealed SVR rate of 90%.[19]

Although HCV genotype 4 was considered the 'most difficult to treat' genotype after the introduction of specific HCV genotype1 protease inhibitors boceprevir and telaprevir in 2011, the approval of sofosbuvir (SOF), simeprevir (SIM) and daclatasvir (DCV) significantly improved the response rates.[20] Our data revealed higher SVR rates for combined SIM/SOF therapy for genotype IV patients compared to

TABLE 3 Characteristics of patients with treatment failure (n=372)

	Discontinuation group (n=97)	Nonresponders (n=150)	Relapsers (n=125)	Total (n=372)	*P* value
Age (/years)*	56.04 ± 8.46	54.20 ± 9.03	54.17 ± 8.40	54.67 ± 8.69	.19
Gender†					
Males	57 (58.8%)	83 (55.3%)	83 (66.4%)	223 (59.9%)	.17
Females	40 (41.2%)	67 (44.7%)	42 (33.6%)	149 (40.1%)	
BMI*	29.37 ± 5.78	30.32 ± 5.64	30.10 ± 5.94	30.03 ± 5.76	.57
Diabetes Mellitus†	19 (19.6%)	14 (9.3%)	19 (15.2%)	52 (14%)	.07
Hypertension†	3 (3.1%)	9 (6%)	3 (2.4%)	15 (4%)	.32
HCC†	0 (0.0%)	1 (0.7%)	1 (0.8%)	2 (0.5%)	.45
Hepatic encephalopathy†	2 (2.1%)	1 (0.7%)	0 (0.0%)	3 (0.8%)	.42
Treatment history†					
IFN naiive	88 (90.7%)	130 (86.7%)	105 (84.0%)	323 (86.8%)	.34
IFN experienced	9 (9.3%)	20 (13.3%)	20 (16.0%)	49 (13.2%)	
HCV RNA (IU) log 10*	5.38 ± 1.03	5.64 ± 0.83	5.44 ± 0.82	5.50 ± 0.89	.06
ALT (IU/L)*	56.28 ± 42.34[a]	57.98 ± 31.35[a]	70.15 ± 46.85[b]	61.63 ± 40.37	.01
AST (IU/L)*	69.09 ± 47.94	67.91 ± 40.73	78.76 ± 43.14	71.86 ± 43.67	.09
AFP (IU/L)*	24.56 ± 69.30	14.03 ± 20.17	19.39 ± 37.15	18.57 ± 42.95	.26
Albumin (g/dL)*	3.65 ± 0.56	3.81 ± 0.60	3.69 ± 0.54	3.73 ± 0.57	.07
Total Bilirubin (mg/dL)*	1.17 ± 0.50	1.03 ± 0.66	1.05 ± 0.49	1.07 ± 0.57	.15
Indirect Bilirubin (mg/dL)*	0.62 ± 0.23	0.64 ± 0.30	0.63 ± 0.23	0.63 ± 0.26	.95
WBC×10^3/mm^3*	5.41 ± 2.24	6.69 ± 6.99	5.59 ± 1.75	5.99 ± 4.72	.05
HG (G/L)*	12.72 ± 1.60[a]	13.29 ± 1.79[b]	13.23 ± 1.67[b]	13.12 ± 1.71	.03
Platelets×10^3/mm^3*	125 ± 68[a]	147 ± 61[b]	133 ± 51[ab]	136 ± 60	.02
PC (%)*	79.12 ± 14.37	81.90 ± 12.56	78.35 ± 16.29	80.00 ± 14.45	.17
INR*	1.23 ± 0.20[a]	1.18 ± 0.17[b]	1.18 ± 0.15[b]	1.19 ± 0.17	.04
Creatine (mg/dL)*	0.95 ± 0.66	0.83 ± 0.23	0.84 ± 0.20	0.86 ± 0.38	.05
E-CrCl*	90.15 ± 32.22[a]	110.90 ± 40.45[b]	124.17 ± 52.74[a]	109.41 ± 43.86	.01
Glucose (mg/dL)*	101.65 ± 28.83	97.90 ± 24.27	101.53 ± 28.81	100.13 ± 27.10	.47
TSH*	1.96 ± 1.46	1.94 ± 1.31	1.81 ± 1.29	1.90 ± 1.33	.70
Ultrasound†					
Liver cirrhosis	47 (48.5%)	74 (49.3%)	84 (67.2%)	205 (55.1%)	.02
Splenomegaly	29 (63.0%)	35 (44.9%)	32 (38.6%)	96 (46.4%)	.06
FIB4*	5.57 ± 4.15[a]	4.14 ± 3.18[b]	4.64 ± 2.95[b]	4.69 ± 3.43	.01
Stiffness/Kps*	22.07 ± 13.23	17.96 ± 7.91	22.96 ± 19.07	19.94 ± 12.75	.57
Varices in upper endoscopy†	16 (16.5%)	14 (9.3%)	7 (5.6%)	37 (9.9%)	.05
Patient group†					
Difficult to treat	74 (76.3%)	108 (72.0%)	107 (85.6%)	289 (77.7%)	.02
Easy to treat	23 (23.7%)	42 (28.0%)	18 (14.4%)	83 (22.3%)	

*Data are given in mean and standard deviation.
†Data are given in number of cases (%).
Different letters in row(s) mean significant difference at the level of 0.05.

the use of the same combination in HCV genotype1 group studied in TRIO real life study which showed SVR12 of 87%-88% in noncirrhotic (IFN experienced-naive) and 75%-76% of cirrhotic patients (IFN experienced-naive).[21] While, in our cohort; SVR12 was 96% & 93% in noncirrhotics and cirrhotics respectively.

Abdel-Razek and Waked in 2015 suggested that the potency of second generation DAA might lead to minimize the role of predictors of response to PEG-IFN/RBV therapy including genotype, viral load, race, IL28B, metabolic syndrome, obesity and age. However, they still suggested that advanced fibrosis and cirrhosis may be a determining

TABLE 4 Causes of discontinuation in discontinuation group (n=97)

Causes of discontinuation			Number (97)
Mortality	Total number		23 (24%)
	Weeks	W2	1 (4.34%)
		W4	20 (86.95%)
		W8	2 (8.69%)
		Undefined	1 (4.34%)
Hepatic decompensation			65 (67.01%)
Complicated HCC			4 (4.12%)
Angiomatous oedema (Drug hypersensitivity)			1 (1.03%)
Haematological complications			3 (3.09%)
Ischaemic heart disease			1 (1.03%)

factor, and will probably require more potent combinations or longer treatment durations.[22] In our study, male gender, lower baseline albumin, platelet count and higher baseline INR and AST were significantly associated with treatment failure as these factors might be associated with more advanced liver fibrosis.

This observation matches with results found by Kanda and colleagues who found that AST, AFP, Liver stiffness together with previous treatment, IL28B rs8099917 and completion of treatment for 12 weeks contributed to achievement of higher SVR in simprevir treated patients.[23]

Cirrhotic patients have a priority in treatment in this Egyptian National Programme in spite of significant lower SVR compared with noncirrhotics. In this study, cirrhotic patients presented (41.2%) of the population treated. They showed significantly lower SVR. SVR rates in difficult and easy to treat population were 93%, and 96% respectively, with $P<.01$). This difference in SVR between cirrhotics and noncirrhotics was expected in advance as this was mentioned by the trial done by Doss and colleagues who included 103 Egyptian patients with genotype 4 treated with SOF and RBV for 12 or 24 weeks. Cirrhotic patients represented 17% of their study population, and showed lower SVR compared with noncirrhotics (78% vs 93%).[5]

In this study, 372/6211 (5.9%) patients did not achieve SVR12, including 97 (1.6%) discontinued their treatment mainly due to hepatic decompensation. Mortality due to liver failure was reported in 23/6211 cases (0.37%). Higher Fib-4 and INR, with lower haemoglobin, platelets and E-Cr clearance were significantly associated with discontinuation of treatment among failure groups. Occurrence of hepatic decompensation in such group of patients may be related to their baseline advanced liver disease. This raises concerns about Simeprevir safety in cirrhotics.

In this study, relapse rate was 2% (125/6211), most of them (107 patients) (85.6%) were difficult to treat, however, this relapse rate was much lower than observed in other IFN free based combinations as Sofosbuvir plus ribavirin, *Ruane and colleagues* reported a relapse rate of 18.33% for Sofosbuvir-ribavirin combination.[24]

We can conclude that oral regimen of simeprevir/sofosbuvir combination is an effective and well tolerated regimen for patients with chronic HCV genotype 4, and it has better SVR with less relapse rates than other combinations. We also recommend further studies concerning cirrhotic patients as regard treatment duration and safety concerns.

CONFLICT OF INTEREST

The authors do not have any disclosures to report.

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