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Sofosbuvir-based treatment regimens: real life results of 14 409 chronic HCV genotype 4 patients in Egypt

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SUMMARY

Background
Chronic hepatitis C virus infection is one of the most important health problems in Egypt. The Ministry of Health's National Treatment Programme introduced sofosbuvir-based therapy in October 2014.

Aim
To assess the clinical effectiveness and predictors of response to SOF-based treatment regimens, either dual therapy, with SOF/ribavirin (RBV) for 6 months or triple therapy with SOF/peg-IFN-alfa-2a/RBV for 3 months, in a cohort of patients treated in National Treatment Programme affiliated centres in Egypt.

Methods
Between October 2014 and end of 2014, patients who were eligible for treatment were classified according to their eligibility for interferon therapy: Group 1 (interferon eligible) were treated with triple therapy for 12 weeks and Group 2 (interferon ineligible) were treated with dual therapy for 24 weeks. Difficult to treat patients included those with F3-F4 on Metavir score, Fib-4 >3.25, albumin ≤3.5, total Bilirubin >1.2 mg/dL, INR >1.2 and platelet count <150 000 mm^3.

Results
Twelve weeks post-treatment data were available on 14 409 patients; 8742 in group 1 and 5667 in group 2. In group 1, the sustained virological response at week 12 (SVR12) was 94% and in group 2 the SVR12 was 78.7%. Multivariate logistic regression analysis in which treatment failure is the dependent variable was done. Male gender, being a difficult to treat patient and previous interferon therapy were significant predictors of non-response in both treatment groups.

Conclusion
Results of sofosbuvir-based therapies in Egypt achieved similar rates of SVR12 as seen in phase III efficacy studies.

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INTRODUCTION

Chronic hepatitis C virus (HCV) infection affects an estimated 170 million people worldwide.[1] Data from the Egypt Demographic and Health Survey[2, 3] estimated the prevalence of HCV viraemia to be 7.3% in 2013 with predominance of genotype 4.[4]

Optimal therapy for patients with hepatitis C virus genotype 4 (HCV-4) infection is changing rapidly; the standard of care for a long time has been a combination of pegylated interferon (PEG-IFN) and ribavirin (RBV), with modest response rates and considerable adverse events.[5]

Recent advances in drug development have led to a number of direct anti-viral agents (DAAs) which deliver high rates of SVR with substantial improvements in the side effect profiles.[6] One of these drugs, sofosbuvir (SOF), a potent inhibitor of the HCV NS5B polymerase, has recently been approved for the treatment of HCV in Egypt.

The efficacy of SOF-based treatment regimen has been evaluated in phase II and phase III trials demonstrating that sofosbuvir has pangenotypic activity against HCV genotypes 1, 2, 3, 4, 5 and 6. Furthermore, the combination of SOF with PEG-IFN and RBV in genotypes 1, 4 and 6 increases the SVR12 rate with 12 weeks duration of therapy.[7, 8]

Our aim was to assess the clinical effectiveness of the SOF-based treatment regimens (both SOF/RBV (dual therapy) for 6 months or SOF/peg- IFN-alfa-2a/RBV (triple therapy) for 3 months) delivered by the National Treatment Programme affiliated centres, Ministry of health in Egypt and to demonstrate the predictors of response in our chronic HCV genotype 4 Egyptian patients.

PATIENTS AND METHODS

Patients

All patients were enrolled in National Treatment Programme for Hepatitis C that was launched in September 2014 to provide treatment with new DAAs. This programme was delivered by more than 50 treatment centres affiliated to National Committee for Control of Viral Hepatitis (NNCVH) that was established by Ministry of Health to face Hepatitis C in Egypt. All included patients had Chronic HCV genotype 4 infection. Patients were enrolled during the period between October 2014 until the end of year 2014. During that period, priority was given for those with advanced liver fibrosis (F3-F4) confirmed by histopathological reading of a liver biopsy or liver stiffness measurements ≥9.5 kPa and/or Fib-4 score >3.25.

Patients were followed up to 12 weeks post treatment. Analysis of treatment outcomes and the factors influencing treatment failure were analysed from the first cohort of 14 409 patients who completed treatment and follow-up.

The data were collected from National Network for Treatment Centers (NNTC) database.

All patients whose treatment outcome was available were included. Patients who were missed for nonmedical cause were excluded. Patients with decompensated liver disease, Child-Pugh B and C cirrhosis, ascites or history of ascites, hepatic encephalopathy or history of hepatic encephalopathy, hepatocellular carcinoma, unless disease free 4 weeks after a potentially curative intervention (no evidence of activity by dynamic imaging (CT or MRI) and no extrahepatic malignancy except after 2 years of disease free interval), serum creatinine >2.5 mg/dL, pregnancy and poorly controlled diabetes (HbA1c ≥8), INR ≥1.7, serum albumin <2.8 g/dL, total serum bilirubin ≥3 mg/dL, platelets <50 000/mm^3 were excluded from both treatment regimens.

Patients were categorised in to two groups: Group 1 who were treated with a combination treatment of SOF, RBV and peg-IFN-alfa- (Triple therapy) for 12 weeks (8742 patient). Group 2 who were treated with SOF and RBV (Dual Therapy) for 24 weeks (5667 patient).

Patients were included according to the criteria of the approved treatment recommendation (EASL 2014).[9]

Patients were considered eligible for IFN if they met the following criteria: age range from 18 to 60 years, total bilirubin ≤1.2 mg/dL, albumin >3.5 g/dL, INR ≤1.2, haemoglobin ≥13 g/dL for males and ≥12 g/dL for females, TLC ≥4000/mm, ANC ≥1500/mm, platelet count ≥150 000/mm with absence of autoimmune diseases, thyroid diseases, unstable cardiac disease, unstable neuropsycatric disorders, oesophageal and or gastric varices. These patients were treated with a combination of SOF, RBV and PEG-IFN (Triple therapy) for 12 weeks Patients who did not fulfil these criteria were considered interferon ineligible and were treated with SOF and RBV (Dual Therapy) for 24 weeks.

Patients who were treated by triple therapy received PegIFNalpha+ribavirin (weight based; 1200 mg if ≥75 kg or 1000 mg if <75 kg of body weight) + sofosbuvir 400 mg/day for 12 weeks.

And those who were treated by dual therapy received sofosbuvir 400 mg/day + ribavirin (weight based;

1200 mg if ≥75 kg or 1000 mg if <75 kg of body weight) for 24 weeks.

Patients were also categorised into easy and difficult to treat groups, 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.

Clinical investigations

Liver cirrhosis was confirmed by, liver histology within 2 years or by fibroscan evaluation with stiffness ≥14.5 kPa and/or Fib 4 >3.25.

Liver stiffness measurements were performed whenever possible using ultrasound elastography (FIBROSCAN 502, ECHOSENSE, Paris, France). Ten valid measurements were performed, and the median of liver stiffness expressed in kPa was reported. Only examinations with a success rate of >60% and an interquartile range (IQR) <30% were included in this study and were considered reliable and cut off 9.5 kPa was considered for advanced fibrosis.[10]

The FIB4 score was calculated using Sterling's formula[11]

$$\text{Age (years)} \times \text{AST[IU/L]}/(\text{PLT}[10^9/\text{L}] \times (\text{ALT[IU]})$$

Serum HCV-RNA was measured using the Cobas Ampli Prep/Cobas TaqMan HCV-RNA assay ((Roche Diagnostics; Pleasanton, CA, USA) with a lower limit of detection of 15 IU/mL at baseline, week 4, end of treatment, and 12 weeks of follow-up after end of treatment. SVR12 is defined as the absence of detectable viraemia 12 weeks after completion of therapy.

Study design

This is a, retrospective, multicentre study of clinical effectiveness with the primary endpoint being the percentage of patients achieving SVR12 in each group.

Written informed consent was obtained from each patient included in the study and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee.

Statistical analysis

Given the differences in disease stage and eligibility for interferon between the two groups of patients, the analysis of factors influencing treatment failure was undertaken separately for the two groups. In univariate analysis, comparison of baseline characteristics with *t*-student's test for quantitative data or chi-square test for categorical data using SPSS 17 software (SPSS,

Table 1 | Characteristic of both groups

	Triple (8742)Group 1(*N*, %)	SOF/RIB (5667)Group 2(*N*, %)	*P* value
Responders (SVR 12)	8217(94%)	4458(78.7%)	<0.01
Nonresponders	139 (1.6%)	91 (1.6%)	
Relapsers	386 (4.4%)	1118 (19.7%)	
Age years (mean ± s.d.)	51.63 ± 8.5	54.4 ± 7.8	<0.01
Male	5045 (57.7%)	3175(56%)	0.4
Previous treatment failure	2381 (27.2%)	1119 (19.7%)	<0.01
BMI (mean ± s.d.)	29.3 ± 4.8	29.6 ± 4.6	0.03
Labs (mean ± s.d.)			
HB g/dL	13.9 ± 2	13.04 ± 1.8	<0.01
Platelets $\times 10^3/mm^3$	177 ± 57	112 ± 61	<0.01
WBC $\times 10^3/mm^3$	6.9 ± 6.7	5.5 ± 5.3	<0.01
Creatinine clearance mL/min	118.6 ± 49	111 ± 35	0.03
HbA1c	6.9 ± 5	6.7 ± 2.3	0.33
Total bilirubin mg/dL	0.81 ± 0.42	1.16 ± 0.64	<0.01
Albumin g/dL	4.09 ± 0.4	3.62 ± 0.5	<0.01
Viral load log 10	5.6 ± 0.85	5.4 ± 0.8	
Fib 4 score (mean ± s.d.)	3.08 ± 7.6	6.7 ± 22.2	<0.01
Liver stiffness kPa (mean ± s.d.)	17 ± 11	24.7 ± 14.7	<0.01
Liver cirrhosis	3089 (35%)	3462 (61%)	<0.01
HCC	3 (0%)	6 (0.1%)	

Chicago, IL, USA). In multivariate analysis, binary logistic regression was done for each treatment protocol separately using variables with a $P < 0.25$ in univariate analysis. In all tests, P value was significant if <0.05.

RESULTS

During the study period 116 828 patients were referred for HCV therapy of whom 44 262 were eligible according to the National Treatment Programme criteria. Treatment was commenced in 28 142 patients. Of the 28 142 patients who commenced therapy 20 324 completed the course of medication and 5915 were subsequently lost to follow-up Our study analysed the data from the first 14 409 patients who completed follow-up to 12 weeks post HCV treatment. SVR12 rates were 94% and 78.7% in Group 1 and Group 2, respectively.

The characteristics of both groups are shown in Table 1. Due to the inclusion criteria virtually all of the patients with cirrhosis, those with higher FIB4 values and those with high liver stiffness values were enrolled in the dual therapy.

Among the 139 nonresponders (NR)in group 1 there were 26 patients who discontinued treatment due to serious adverse events (SAEs), mostly hepatic decompensation which occurred in 22 patients, haematological complications (anaemia or thrombocytopenia) in three patients and development of HCC in one patient. Renal impairment was reported in one patient.

Among the 91 NR in group 2, there were 65 patients who discontinued treatment. Among these patients, four patients ceased treatment for haematological complications, two patients due to development of HCC and one patient due to renal impairment. Mortality occurred in two cases.

Predictors of response in both groups are shown in Table 2. SVR 12 was achieved in both groups among patients who are naive, females, with lower liver stiffness values, higher albumin and platelets levels and low bilirubin levels. Baseline viral load had no impact on the response to therapy in either groups (Table 2).

Among cirrhotic patients, SVR 12 rates were 92.5% and 76% in group 1 and group 2 respectively.

Among treatment-experienced patients, SVR 12 rates were 92% and 69 in group 1 and group 2 respectively (Table 2, Figures 1 and 2).

Multivariate logistic regression analysis was done in both groups, with the failure of response as the dependent variable. Male gender, being a difficult to treat patient and previous interferon therapy were significant predictors of nonresponse in both treatment groups. (Table 3).

Table 2 | SVR 12 in both groups and predictors of response

	Triple (*n*, %) (group 1)			Dual (*n*, %) (group 2)		
	Responders 8217 (94%)	Nonresponders 525 (6%)	*P* value	Responders 4458 (78.7%)	Nonresponders 1209 (21.3%)	*P* value
Age (years) (mean ± s.d.)	52 ± 8	51 ± 8	0.3	55 ± 8	54 ± 8	0.02
BMI (mean ± s.d.)	29 ± 4.8	30 ± 4.4	<0.01	29.6 ± 4.8	29.6 ± 4.2	0.9
Male	4713 (57.4%)	332 (63.2%)	0.01	2335 (52.4%)	840 (69.5)	<0.01
Previous treatment failure	2192 (26.7%) *(92%)	189 (36%) *(8%)	0.01	777 (17.4%) *(69%)	342 (28.3%) *(31%)	<0.01
FiB4 (mean ± s.d.)	2.9 ± 5.8	4.5 ± 21.2	<0.01	6.5 ± 23.9	7.2 ± 14.4	0.3
stiffness (mean ± s.d.)	16.7 ± 10.8	20.7 ± 13	<0.01	23.4 ± 14.7	30 ± 13)	<0.01
Liver cirrhosis	2858 (34.8%) †92.5%	231 (44%) †7.5%	<0.01	2626 (59%) †(76%)	836 (69%) †(24%)	<0.01
Albumin g/dL	4.09 ± 0.5	3.9 ± 0.45	<0.01	3.6 ± 0.6	3.4 ± 0.5	<0.01
HB g/dL	13.9 ± 2	14 ± 1.56	0.4	13 ± 1.5	13.2 ± 1.7	1.2
Platelets $\times 10^3/mm^3$	178 ± 57	163 ± 47	<0.01	115 ± 60	102 ± 65	<0.01
WBC $\times 10^3/mm^3$	6.9 ± 6.7	6.8 ± 6.5	0.7	5.6 ± 5.4	5.2 ± 4.5	0.023
Bilirubin mg/dL	0.8 ± 0.4	0.88 ± 0.48	0.01	1.1 ± 0.6	1.4 ± 0.7	<0.01
HCV-RNA-log10	5.6 ± 0.85	5.6 ± 0.87	0.8	5.4 ± 0.9	5.5 ± 0.8	0.06
Difficult to treat‡	7390 (90%)	496 (95%)	<0.01	4402 (99%)	1208 (100%)	<0.01
HCC	3 (0%)	0 (0%)	0.44	2 (0%)	4 (0%)	0.03

* Among treatment-experienced patients, SVR in triple therapy 92%, while it is 69% in dual therapy.

† Among cirrhotics, SVR in triple therapy 92.5%, while it is 76% in dual therapy.

‡ Difficult to treat patients who fulfilled either cirrhotic pattern by US, and/or had oesophageal varices, previous liver biopsy revealed F3 or F4 by METAVIR, Fib-4 >3.25, serum albumin <3.5 g/dL, or total bilirubin >1.2 mg/dL.

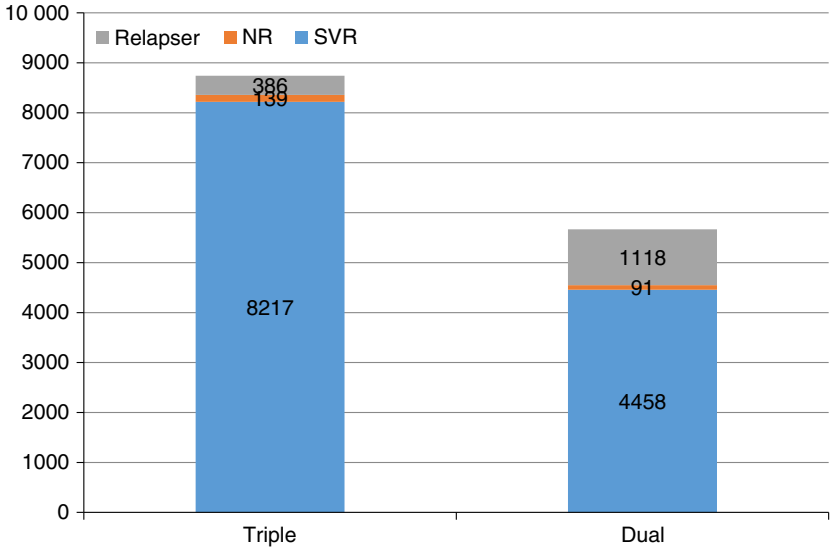

Figure 1 | Response at week 12 post treatment among triple and dual therapy groups.

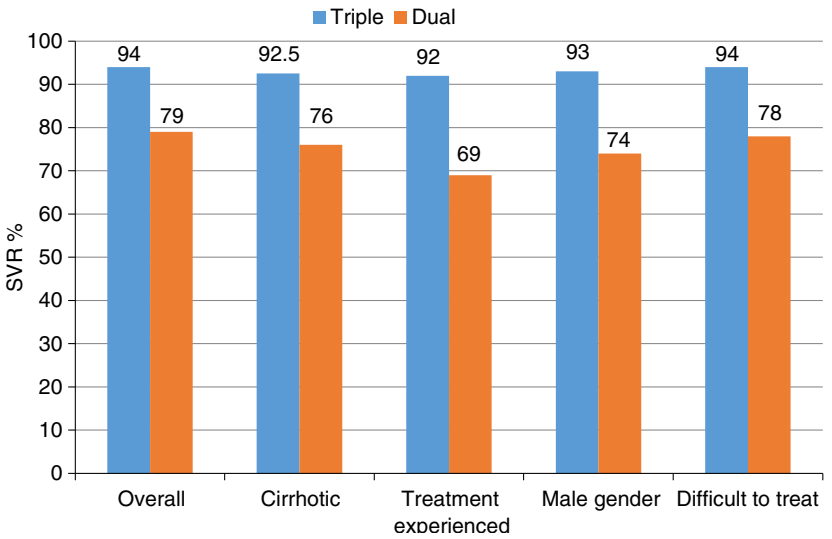

Figure 2 | Response among different groups.

DISCUSSION

Continuous efforts from the National committee of control of viral hepatitis and the Ministry of Health ensured that Sofosbuvir became available in 2014 at prices appropriate for the scale of the epidemic of HCV and for the economic situation in Egypt. Nevertheless, due to the large number of patients with HCV in Egypt, the high cost and the limited amounts of drugs available, it was not possible to treat all patients immediately and the decision was made to start with those patients who had advanced liver fibrosis (F3-F4) as recommended by EASL 2014[9] and AASLD 2015.[12] Our results therefore reflect the severity of liver disease in this cohort of patients.

HCV genotype4 was previously considered a difficult to treat genotype. Using Peg-IFN/RIB as standard of care for 48 weeks SVR24 rates which were higher than in genotype 1 but substantially lower than those seen in patients with genotype 2 and 3 patients. Overall, SVR rates for genotype 4 in Egypt and the Middle East were about 60–69%.[13–15]

SOF-based therapies are the novel standard of care with high anti-viral activity, broad genotypic coverage and a high barrier to resistance.[16, 17] In genotype 4 infected patients SVR12 rates for triple therapy with SOF/PEG-IFN/RBV were 96%[8] in clinical trials. There is substantially less data on treatment outcomes for genotype 4 infected patients using dual therapy with SOF/RBV for 24 weeks. Doss *et al.*, 2015 reported SVR 12 rate of 78% for cirrhotic patients and 93% in patients without cirrhosis.[18]

Treatment outcomes in the real world do not necessarily follow those seen in efficacy trials used for licensing new treatments. However, in HCV a number of recent publications from real world cohorts have reported

Table 3 | In multivariate regression analysis, in which treatment failure is the dependent variable

	Triple therapy (group 1)			Dual therapy (group 2)		
	OR	*P* value	95% CI OR	OR	*P* value	95% CI OR
Male gender	1.22	0.04	1.0–1.5	2.01	<0.01	1.75–2.31
Difficult to treat	1.86	0.001	1.3–2.7	16.31	0.01	2.24–118.3
Baseline viraemia >6 × 10^5	1.14	0.16	0.95–1.36			
Previous treatment failure	1.48	<0.01	1.23–1.79	1.79	<0.01	1.54–2.08

SVR12 rates in the same order of magnitude as those seen in pivotal trials.[19, 20] The real world cohorts arising from centres in the USA and Europe are dominated by patients infected with genotypes 1a and 1b and to a lesser extent genotype 3. In contrast genotype 4 infection dominates in Egypt and this is the first large scale real world cohort to be reported. It is reassuring to note that the SVR12 results achieved in patients who completed follow-up were in the same order of magnitude as those seen in clinical trials. Our results using the triple therapy regimen were very close to the results of the phase 2 trials (Photon and Atomic) using the same drugs.[7, 21] Furthermore, in the triple therapy group the SVR12 rates were equal to that reported in the phase 3 NEUTRINO trial with predominantly genotype 1 or 4 HCV infection.[16]

In the phase 2 trials (QUANTUM and ELECTRON) using SOF/RBV dual therapy, SVR12 rates were 56% and 88% respectively. Extending the treatment duration to 24 week as in our study showed no obvious benefit in a subgroup of patients in the QUANTUM and NIH SPARE studies.[22, 23] The difference between our results and these trials may be attributed to different genotypes and the absence of treatment-experienced patients in previous trials.[22, 23]

Results of the FUSION trial that used the same duration (24 weeks) in genotypes 2 and 3 led to significant improvement of SVR from 56–73%.[24]

Doss *et al.*, 2015 suggested that SOF/RBV for either 12 or 24 weeks is successful in treating treatment-naïve and treatment-experienced Egyptian patients with genotype 4 HCV. The rate of SVR12 was higher in the group receiving 24 weeks (90%) vs. 12 weeks (77%) of therapy with 17% cirrhotic at baseline.[18] The low number of cirrhotic patients in their study would possibly explain the difference.

By multivariate regression analysis and as reported in other studies,[16, 18, 25] liver cirrhosis evidenced by any of criteria we included for the group of 'difficult to treat' was a predictor of nonresponse in our population. A European study on 60 subjects of Egyptian ancestry with HCV genotype 4 including both treatment naïve or treatment-experienced patients compared SVR rates with either 12 or 24 weeks of treatment with SOF/RBV.[26] As reported in this study, they reported that treatment-naïve patients had higher SVR rates than the treatment-experienced patients.

The main limitation of this study is the low rate of follow-up. Only 72.2% of the 28 142 patients who commenced therapy were followed up to completion of treatment and only 51.2% were followed up to 12 weeks after the end of therapy when the outcome of treatment can be judged. It is not possible to estimate the treatment success rate in patients who were not followed up but it is reasonable to assume that it may not be as high as the rates seen in patients who were fully adherent to the monitoring regimen.

CONCLUSION

Sofosbuvir-based therapies whether triple or dual show higher rates of SVR compared to that of the previously used SOC. However, it is not possible to assess treatment effectiveness comprehensively as the rate of loss to follow-up is high. There is still a need for further novel DAA s based therapy to have better response rates especially in patients with advanced fibrosis.

AUTHORSHIP

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