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Generic daclatasvir plus sofosbuvir, with or without ribavirin, in treatment of chronic hepatitis C: real-world results from 18 378 patients in Egypt

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Summary

Background: Treatment of chronic hepatitis C using combination of sofosbuvir (SOF) and daclatasvir (DCV) was used in several clinical trials and multicentre studies, which were somewhat limited to genotypes 1-3. The national program in Egypt is using SOF-DCV combination for large scale treatment.

Aim: To assess the efficacy and safety of combined SOF-DCV in treating patients with HCV-G4 in a real-world setting.

Methods: Data and outcome of chronic HCV patients who were treated for 12 weeks with generic medications: DCV 60 mg plus SOF 400 mg ± ribavirin (RBV) within the national hepatitis C treatment program in Egypt are presented. Treatment-naïve patients without cirrhosis were treated without RBV, and those who had cirrhosis or were treatment-experienced (interferon experienced or SOF experienced) received RBV. Efficacy and safety were assessed, and baseline factors associated with sustained virological response at post-treatment week 12 (SVR12) were explored.

Results: During the first 2 months of the programme, 18 378 patients with HCV-G4 started treatment with SOF-DCV with or without RBV. Overall, 95.1% achieved SVR12 (95.4% among patients treated without RBV and 94.7% for patients treated with RBV, $P = .32$). Treatment was prematurely discontinued in only 1.5% of patients. The most common events leading to discontinuation were patient withdrawal ($n = 76$) and pregnancy ($n = 5$). Five deaths occurred within this group.

Conclusions: Real-world experience of generic SOF-DCV in patients with chronic HCV-G4 proved to be safe and associated with a high SVR12 rate, in patients with different stages of fibrosis.

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1 | INTRODUCTION

Chronic hepatitis C virus (HCV) infection is estimated to globally affect 70-100 million people.[1] Genotype 4 infects 10-15 million persons; a large percentage of whom are living in Egypt, where HCV-G4 represents more than 90% of the infected population.[2]

During the last few years, management of HCV became more effective with the appearance of different classes of direct antiviral agents (DAA). They raised the sustained virological responses (SVR) rates from around 40% with pegylated interferon (PEG) and ribavirin (RBV)[3] to more than 90%.[4,5] Different combinations afforded the possibility of interferon-free regimens with unprecedented success rates.[6]

Daclatasvir (DCV) is a potent HCV NS5A replication complex inhibitor which is active against HCV-G4,[7,8] sofosbuvir (SOF) is a pan-genotypic NS5B polymerase inhibitor that showed a good safety profile as well as a high barrier to resistance.[9] The combination of both drugs led to appreciable success rates,[10-13] including patients in different special populations as HIV-coinfected patients, advanced liver diseases, pre- and post-transplant settings and haemodialysis patients.[8,14-21]

In Egypt, the National Committee for the Control of Viral Hepatitis (NCCVH) started a mass treatment program[22] that was initially based on SOF in combination with RBV for a treatment duration of 24 weeks or in combination with PEG and RBV for 12 weeks, during the period from October 2014 till May 2015, with SVR12 rates of 78.4% and 94% respectively.[23,24] This was followed by an era of combined SOF and simeprevir (SMV) therapy that provided an overall 94% SVR12.[25] Starting November 2015, generic SOF+DCV (with or without RBV) became the main line of therapy in the national program, due to a cost saving of more than 80% of the reduced cost of the brand medications that were being used in the program.

Real-world experience has the benefit to overcome limitations of clinical studies. It assesses the actual situation of the drugs without exclusion criteria applied by the studies for optimisation. It truly assesses the efficacy and safety on a large scale of patients. Here, we present the real-world experience of using SOF-DCV regimen with or without RBV in the management of HCV genotype 4, which has been scarcely represented in previous clinical trials.

2 | PATIENT AND METHODS

2.1 | Study population

This report presents data prospectively collected from 18 378 viremic HCV patients with chronic liver disease, mostly infected with HCV-G4. They were consecutively recruited from patients who started treatment during the first 2 months of the introduction of the generic forms of SOF and DCV (in November and December 2015), in the viral hepatitis specialised treatment centres affiliated to the NCCVH in Egypt where the generic medications were first introduced.

The national treatment program in Egypt included all patients ≥18 years old with chronic HCV infection, and although initially treatment with DAAs was prioritised to patients with advanced fibrosis (F3 and F4), starting May 2015, patients were included with all stages of liver fibrosis (F0-F4). Patients with HBV/HCV co-infection, patients with hepatocellular carcinoma more than 4 weeks after complete ablation (as confirmed by dynamic CT or MRI) and patients with relapse after previous interferon-based or DAA-based regimen not containing an NS5A inhibitor were permitted. Exclusion criteria included clinically evident hepatic decompensation (presence of ascites and/or encephalopathy) calculated creatinine clearance (Cr Cl) ≤30 mL/min, extrahepatic malignancy (except after 2 years of disease-free interval), pregnancy and refusal to comply with contraception (for female patients and partners of male patients during the child-bearing period).

Fibrosis stage was evaluated using data from liver biopsy, or results of Fibroscan or FIB-4 score[26] at any time prior to enrolment.

Patients were assigned to two treatment groups: an "easy-to-treat" group included patients who were treatment naïve who did not have cirrhosis and had compensated liver biochemical parameters: serum bilirubin ≤1.2 mg/dL, serum albumin ≥3.5 g/dL, INR ≤1.2, and platelet count ≥150 000/cmm. They were treated with SOF-DCV for 12 weeks without RBV. Patients who had previously failed interferon or PEG based therapy, or SOF-RBV±PEG, or SOF-SMV were considered "difficult-to-treat" and were treated with SOF-DCV-RBV for 12 weeks regardless of the fibrosis stage. Fibrosis stage was not assessed systematically, but if available, patients with biopsy showing cirrhosis, liver stiffness by Fibroscan of 12.5 kPa or more, or Fib-4 > 2.5 were considered "difficult-to-treat" and were treated with SOF-DCV-RBV. Patients were also considered "difficult-to-treat" if they had serum albumin <3.5 g/dL, bilirubin >1.2 mg/dL, INR>1.2, and/or platelet count <150 000/cmm, regardless of previous treatment history or fibrosis stage (if available). "Difficult-to-treat" patients who had a contraindication for RBV use (haemoglobin <10 g/dL, haemoglobinopathies as thalassaemia and sickle-cell anaemia, or hypersensitivity to the drug) were treated with SOF-DCV for 24 weeks, and their results are not included in this report.

Baseline laboratory tests including a PCR test for viral load were accepted from external labs if performed during the preceding 3 months. All patients were entitled to free baseline, on-treatment, and post-treatment hematological, biochemical and viral load tests on the expense of the Ministry of Health (MoH). However, tests performed elsewhere in private labs during and after treatment were accepted and not repeated. Around 40% of baseline PCRs and more than 60% of on-treatment and post-treatment lab tests were performed at MoH labs, where the lower limit of detection (LLOD) of HCV-RNA was 12 IU/mL. Baseline HCV-genotyping was not performed, as more than 90% of HCV infected patients in Egypt are infected with HCV-G4, and the remaining patients are infected with HCV-G1, with genotypes 2, 3, 5 and 6 almost non-existent,[1,2] and this analysis assumes that almost all patients are infected with HCV-G4.

The study was conducted in accordance with the declaration of Helsinki and was approved by the Ethics Committee of the NCCVH. All patients treated in the national program sign an informed consent before starting treatment allowing the use of their clinical data and

lab results for reports and publications (those who do not sign the consent received treatment but their data were not included).

2.2 | Medications

Generic SOF and DAC were supplied to the MoH centres by five of the 15 local manufacturers according to a tender concluded in September 2015, where the five companies with the best manufacturing facilities were chosen (AUG Pharma, Magic Pharma, Marcyrl, Pharmed, and Pharco), and the price was set at the lowest price offered (EGP 1710 for a 12-week supply of both SOF and DAC [equivalent to US$ 235 at the prevailing exchange rate at the time]). Each company supplied medications exclusively to a number of centres according to its production capacity, so that each patient received medications from the same manufacturer through treatment. The centres included in this analysis represent the five manufacturers. RBV was a locally produced generic (Amriya Pharmaceutical, Egypharma, GNP Pharmaceuticals, Mash Pharmaceuticals, Minapharm, October Pharma, Pharco, and T3A).

SOF was given in a dose of 400 mg/day, DCV in a dose of 60 mg/day, both in a single daily dose and patients were advised to take them after breakfast. RBV was supplied in 200 mg capsules: and the recommended dose was 1200 mg daily if the patient's weight was more than 75 kg, and 1000 mg daily if the patient weight was less than 75 kg, given in two divided doses. RBV dose modification or discontinuation was allowed at the discretion of the treating physician according to change in haemoglobin. Potential drug-drug-interactions with patients' medications were checked using the University of Liverpool application on smart phones (Liverpool HEP iChart) or the website (http://www.hep-druginteractions.org/checker). Drugs contraindicated with SOF or DCV were discontinued or changed if possible, or patients' treatment was deferred. No dose adjustments were attempted for SOF or DCV. Records of co-medications were not analysed for this report.

2.3 | Endpoints

The primary efficacy endpoint was the proportion of patients achieving a SVR at 12 weeks after the end of therapy defined as HCV-RNA below the assay's LLOD measured at 12 weeks after the end of treatment (EOT; SVR12). Secondary efficacy endpoints included EOT virological response, defined as HCV-RNA below the assay's LLOD measured at the EOT. Virological failure included relapse (HCV-RNA $\geq$LLOD during any post-treatment follow-up visit in patients with HCV-RNA$<$LLOD at the EOT, virological nonresponse (HCV-RNA not reaching $<$LLOD during treatment, or HCV-RNA $\geq$LLOD at EOT), and treatment discontinuation due to adverse events (AEs).

2.4 | Safety assessments

Safety endpoints included graded AEs, serious AEs, discontinuations due to AEs, deaths, and laboratory abnormalities.[27]

All patients were included in the safety assessment. All assessments were performed at each individual centre based on standard local practice and recommendations of the NCCVH. Laboratory tests for assessments of biochemical and hematological parameters, and safety assessments were recommended at baseline, treatment week 4, EOT (week 12) and post-treatment week 12.

2.5 | Covariates

Data about the following variables were obtained from all patients included in the analyses.

2.5.1 | Demographics and clinical data

Age, gender, body mass index (BMI), previous treatment status (naïve or experienced) and if treatment experienced, details about previously administered medications.

2.5.2 | Laboratory, imaging, and endoscopic data

Data were collected at baseline, and included blood count, AST, ALT, bilirubin, albumin, INR, creatinine and calculated creatinine clearance, HBsAg, alpha-fetoprotein (AFP), and HCV-RNA. Data from abdominal ultrasonography reports included echo pattern of the liver, the presence of hepatic focal lesions, ascites, splenomegaly or any other co-morbidities. Endoscopic data included presence or absence of varices.

2.6 | Statistical analysis

The primary population for efficacy and safety analyses included patients who received one dose of either treatment regimens. Data were entered, validated, and analysed using STATA 14 (College Station, TX, USA) software. Patients' demographic and routine laboratory values data were expressed as number (per cent) for binary variables and as *M* ($\pm$SD) or median (interquartile range) for continuous variables. Baseline data were compared according to administered treatment protocol: SOF-DCV and SOF-DCV-RBV. This report does not aim to demonstrate the difference in efficacy between the two treatment regimens, as the patient assignment was not random, and based on pre-set selection criteria according to presence or absence of advanced fibrosis/cirrhosis, abnormal liver tests and previous treatment failure. No sample-size estimation was performed, and the number of patients included was not selected to demonstrate differences between groups. Included patients are those who started treatment during the set time in the centres selected. However, comparisons between groups aimed only at demonstrating the efficacy of SOF-DCV combination in HCV-G4, and the efficacy of the generic medications in different settings. Variables were analysed using either Students' *t*-test or Mann-Whitney test for comparison of two groups whenever appropriate. Chi-squared test was used for comparison of binary variables. Univariate and multivariate adjusted logistic regression analyses were performed to identify baseline

factors associated with SVR12. Data were presented as odds ratios (ORs) with 95% confidence intervals (95% CI). All statistical analyses were based on two-sided hypothesis tests with a significance level of $P < .05$.

3 | RESULTS

3.1 | Patients

Data were available for 18 378 enrolled patients who received treatment with SOF-DCV (n = 10 120) or SOF-DCV-RBV (n = 8258) during the first 2 months of introducing the generic drugs to the national program (November and December 2015). Figure 1 shows the patient's disposition, and the numbers included in each treatment arm. Mean age was 49.4 ± 11.6 years; most patients were females (57.6%) and treatment naïve (93.0%). Baseline data revealed frequent comorbidities, including obesity, diabetes and hypertension (Table 1).

Assignment of treatment was nonrandomised, but was based on previous treatment history, and indicators of the presence of advanced fibrosis or cirrhosis. "Easy-to-treat" patients were treated without RBV, and "difficult-to-treat" patients were treated with SOF-DCV-RBV for 12 weeks. Forty-four treatment-naïve patients with normal laboratory tests were treated as "difficult-to-treat" with RBV in addition to SOF-DCV due to incorrect initial evaluation categorising them as having cirrhosis, and their results are among the 8258 patients in the RBV group, and 395 treatment-experienced patients were incorrectly treated as "easy-to-treat" patients without additional RBV. Despite being an exclusion criterion, 35 patients with ascites were included, 14 patients as "easy-to-treat" and 21 patients as "difficult-to-treat".

As a result of assignment criteria, more patients treated with SOF-DCV-RBV had signs suggestive of advanced liver disease, including higher proportions of patients with coarse liver echo-texture on ultrasound (33.0% vs 16.9%, $P < .001$), ascites (0.3% vs 0.1%, $P = .001$) and oesophageal varices (2.0% vs 0.6%, $P < .001$; Table 1).

3.2 | Efficacy outcomes

Overall, SVR12 was achieved by 95.1% (95% CI 94.8-95.4) of the 18 738 patients in this cohort, while 96.2% (95% CI 95.9-96.4) of

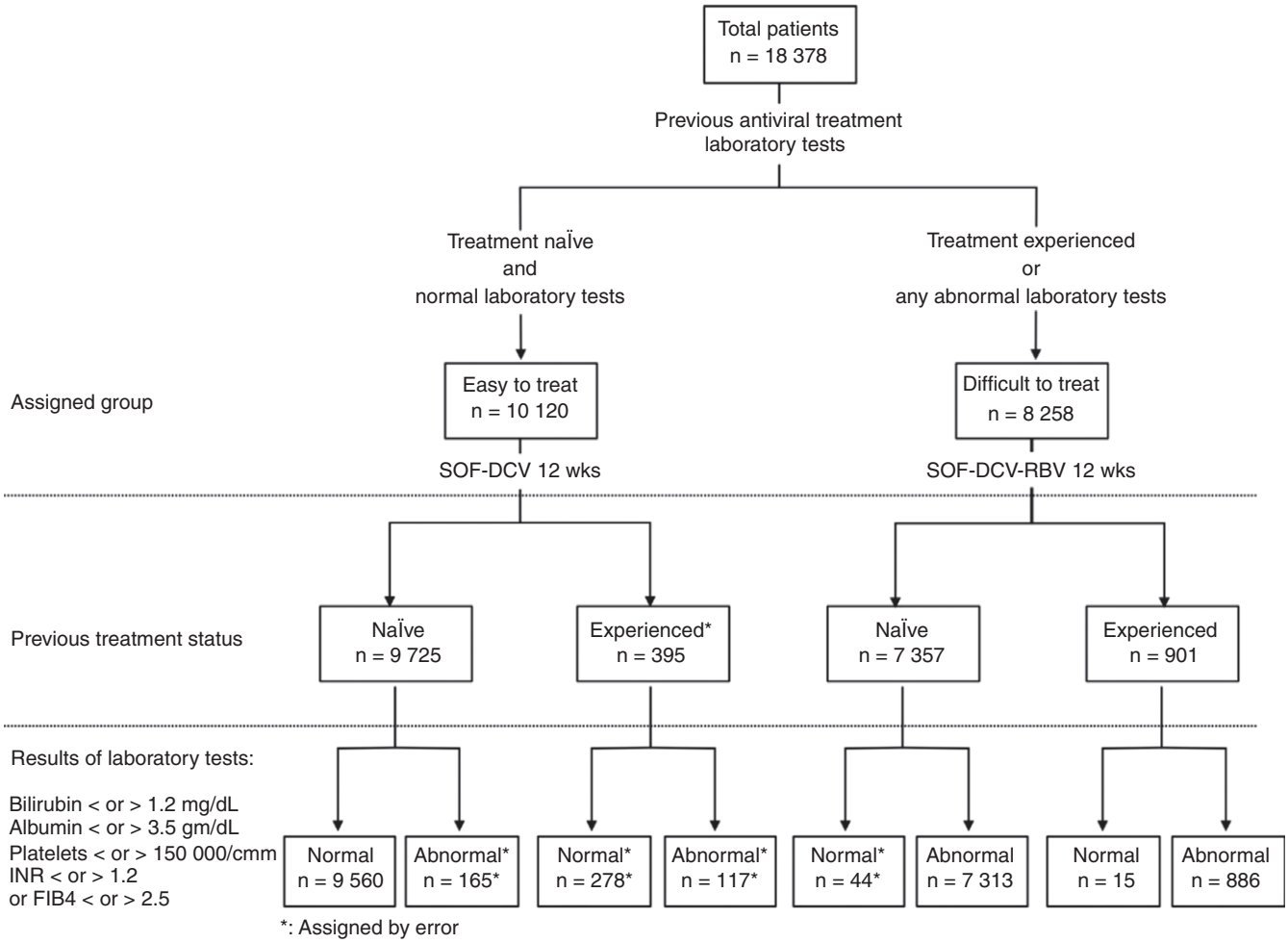

FIGURE 1 Patient disposition

TABLE 1 Baseline characteristics and demographics of studied patients (n = 18 378)

Parameter	SOF-DCV (n = 10 120)	SOF-DCV-RBV (n = 8258)	*P* (SOF-DCV vs SOF-DCV-RBV)
Age (y), *M* ± SD	48.4 ± 11.6	51.6 ± 10.2	
Male, n (%)	4211 (41.6)	3587 (43.4)	
Treatment experienced, n (%)	395 (3.9)	901 (10.9)	
Metabolic data and special habits			
BMI (kg/m^2), *M* ± SD	29.4 ± 5.5	29.7 ± 5.6	
BMI >30, n (%)	2148 (21.2)	2141 (25.9)	
Diabetes, n (%)	863 (8.5)	1050 (12.7)	<.001
Hypertension, n (%)	637(6.4)	686 (8.5)	<.001
Alcohol intake, n (%)	10 (0.1)	8 (0.1)	
Tobacco smoking, n (%)	387(3.8)	319(3.9)	
Laboratory data			
Bilirubin Total (mg/dL) *M* ± SD	0.8 ± 0.5	0.9 ± 0.5	
ALT (ULN:40U/L) *M* ± SD	48.8 ± 33.2	56.3 ± 37.7	
AST (ULN:40 U/L) *M* ± SD	50.33 ± 32.77	62.53 ± 39.92	
Albumin (g/dL) *M* ± SD	4.1 ± 0.5	3.9 ± 0.54	
Albumin>3.5 g/dL, n (%)	9088 (90.3)	5837 (71.0)	
INR	1.1 ± 0.1	1.2 ± 0.2	
WBC (×10^3/mm^3)	6.4 ± 2.1	5.8 ± 2.1	
Haemoglobin (g/dL)	13.3 ± 1.6	13.2 ± 1.7	
Platelets (×10^3/mm^3)	215.4 ± 62.5	163.3 ± 68.9	
Creatinine (mg/dL)	0.8 ± 0.2	0.8 ± 0.2	
Blood glucose	100.6 ± 25.5	103.5 ± 27.5	
AFP, median (IQR)	4 (5)	6 (8)	
HBsAg positive, n (%)	61 (0.7)	41 (0.6)	0.3
HCV PCR $\log_{10}$	5.6 ± 0.9	5.6 ± 0.9	
Ultrasonography data			
Coarse liver echo-texture, n (%)	1707 (16.9)	2726 (33.0)	<.001
Ascites, n (%)	14 (0.1)	21 (0.3)	
Ablated focal lesion, n (%)	14 (0.1)	35 (0.6)	
FIB4, median (IQR)	1.5 (1.2)	2.7 (2.9)	<.001
Varices on endoscopy, n (%)	60 (0.6)	166 (2.0)	<.001

Data are expressed as *M* (±SD), median (IQR), or n (%).
BMI, body mass index; ALT, alanine transaminase; AST, aspartate transaminase; INR, international normalised ratio; WBC, white blood cell count; AFP, alpha fetoprotein; HBsAg, hepatitis B surface antigen; IQR, inter quartile range.

the patients had achieved EOT response and 1.1% relapsed after treatment ended. SVR12 rates were higher among patients treated with SOF-DCV than among those who received SOF-DCV-RBV (95.4% [95% CI: 95.0-95.8] vs 94.7% [95% CI 94.2-95.2] *P* = .035) (Table 2).

Among patients who failed treatment, more patients treated with SOF-DCV-RBV discontinued therapy than those treated with SOF-DCV (2.0% vs 1.0%, *P* < .001), while primary nonresponse occurred slightly more among those treated without RBV (2.6% vs 2.2%, *P* = .14). Relapse rates were similar in both cohorts (*P* = .9; Table 2).

Among patients treated with SOF-DCV-RBV (n = 8258), patients with normal laboratory tests (n = 59) who were treatment experienced (n = 15) all responded to treatment, and those who were treatment naïve and allocated to this group by an error at inclusion (n = 44) had an SVR12 rate of 95.6%. Patients receiving RBV because of the presence of cirrhosis or abnormal liver tests who were treatment naïve (n = 7313) had an SVR12 rate of 94.5%, and those with previous treatment history (n = 886) had an SVR12 rate of 96.2%. No significant differences in SVR12 rates were observed between groups of patients who received SOF-DCV-RBV (*P* = .17; Table 3).

Compared to those who did not achieve SVR12 (n = 905), patients who achieved SVR12 were younger (*P* = .002), more females (*P* < .001), had lower prevalence of diabetes (*P* = .02), lower

TABLE 2 Assessment of treatment efficacy among studied patients (n = 18 378)

Parameter	SOF-DCV (n = 10 120)	SOF-DCV-RBV (n = 8258)	P[a]
End of treatment response			
Number (%)	9761 (96.5)	7910 (95.8)	**.02**
95% CI	96.0-96.8	95.4-96.2	
SVR12 rates			
SVR12, n (%)	9653 (95.4)	7820 (94.7)	**.03**
95% CI	95.0-95.8	94.2-95.2	
Non-SVR12, n (%)	467 (4.6)	438 (5.3)	
Non-SVR12 categories (%)			
Relapse (% of patients with ETR)	108 (1.1)	89 (1.1)	.9
Discontinued	100 (1.0)	166 (2.0)	**<.001**
Nonresponder	259 (2.6)	183 (2.2)	**.14**

[a]SOF-DCV vs. SOF-DCV-RBV.
Bold values represent statistical significance.

ALT ($P < .001$), AST ($P < .001$), bilirubin ($P < .001$), and FIB4 ($P < .001$), and had higher albumin ($P < .001$), haemoglobin ($P = .02$), leucocytes ($P = .01$) and platelets ($P < .001$; Table 4).

Forty-nine per cent (442/905) of patients who did not achieve SVR12 were on-treatment nonresponders, 29.4% discontinued treatment and 21.8% relapsed after the EOT. Baseline clinical and laboratory parameters of patients who failed treatment (nonresponders and those who discontinued or relapsed) are shown in Table 5.

3.3 | Baseline predictors of SVR12

Independent predictors for treatment failure in each treatment group are shown in Table 6. PEG-RBV or SOF-RBV±PEG experienced patients included by error as "easy-to-treat" patients (n = 395) responded to treatment similar to those who were treated with additional RBV (Table 6).

3.4 | Safety and tolerability

Treatment was prematurely discontinued in 1.45% of patients (n = 266), including 5 deaths while on-treatment. All reported deaths were among patients receiving SOF-DCV-RBV and were due to decompensation and liver failure. One hundred SOF+DCV recipients (0.99%) discontinued medications; the most common causes of discontinuation were patient withdrawal (n = 76) or pregnancy (n = 5). The most frequent reported adverse events were hematological (n = 4), decompensation and/or development of ascites (n = 3). Serious adverse events were reported in six patients receiving SOF-DCV. Treatment discontinuation rate was higher (n = 166, 2.01%) among SOF-DCV-RBV recipients; the most common cause was patient withdrawal (n = 136). The most frequent adverse events were decompensation and/or development of ascites (n = 9) and hematological complications (n = 5). Serious adverse events were reported in only three patients receiving DCV-SOF-RBV. Most of

TABLE 4 Baseline characteristics of patients who achieved SVR vs those who failed treatment (nonresponders, discontinued, and relapsed) (n = 905)

	Non-SVR12 (N = 905)	SVR12 (N = 17 473)	P value
Age, M ± SD	50.9 ± 11.1	49.7 ± 11.1	**.002**
Male, n (%)	446 (49.3)	7352 (42.1)	**<.001**
BMI (M ± SD)	29.3 ± 5.6	29.6 ± 5.5	.43
Diabetes, n (%)	116 (12.8)	1797 (10.3)	**.02**
Hypertension, n (%)	55 (6.3)	1268 (7.4)	.23
Treatment naïve, n (%)	853 (94.3)	16 229 (92.9)	.12
Treatment experienced, n (%)	52 (5.8)	1244 (7.1)	
Treatment arm			
SOF/DCV, n (%)	467 (51.6)	9653 (55.3)	**.03**
SOF/DCV/RBV, n (%)	438 (48.4)	7820 (44.8)	
HCV-RNA $\log_{10}$ (M ± SD)	5.6 ± 0.9	5.6 ± 0.9	.51
ALT (M ± SD)	56.9 ± 38.5	51.9 ± 35.3	**<.001**
AST (M ± SD)	63.3 ± 41.0	55.4 ± 36.4	**<.001**
Albumin (M ± SD)	3.9 ± 0.6	4.0 ± 0.5	**<.001**
Total bilirubin (M ± SD)	0.9 ± 0.5	0.9 ± 0.5	**<.001**
WBC (M ± SD)	6.0 ± 2.2	6.1 ± 2.1	**.01**
Haemoglobin (M ± SD)	13.1 ± 1.7	13.3 ± 1.6	**.02**
Platelets (M ± SD)	173.7 ± 71.1	192.9 ± 70.2	**<.001**
INR (M ± SD)	1.1 ± 0.2	1.1 ± 0.2	**<.001**
Coarse liver echo-texture on ultrasound, n (%)	237 (26.2)	4196 (24.0)	.25
FIB4 Median (IQR)	2.33 (2.9)	1.84 (1.9)	**<.001**

Bold values represent statistical significance.

TABLE 3 Treatment efficacy within the SOF-DCV-RBV cohort, n = 8258

	Abnormal laboratory tests[a] (N = 8199)		Normal laboratory tests[b] (n = 59)		
	Experienced (n = 886)	Naïve (n = 7313)	Experienced (n = 15)	Naïve[c] (n = 44)	P value
SVR12, n (%)	852 (96.2)	6911 (94.5)	15 (100)	42 (95.5)	.17
95% CI	94.7-97.2	93.9-95.0	84.7-100	84.5-99.4	

[a]Bilirubin >1.2 mg/dL, albumin <3.5 g/dL, platelets <150 000/cmm or INR >1.2, or FIB4 > 2.5.
[b]Bilirubin <1.2 mg/dL, albumin >3.5 g/dL, platelets >150 000/cmm and INR <1.2, and FIB4 < 2.5.
[c]These patients were assigned by error and should have been assigned to treatment without RBV.

TABLE 5 Baseline characteristics of the patients who did not achieve SVR (n = 905)

	Relapsed (n = 197)	Discontinued (n = 266)	Nonresponder (n = 442)
Age (*M* ± SD)	51.7 ± 9.9	52.35 ± 11.7	49.6 ± 11.1
Male, n (%)	97 (49.2)	123 (46.2)	226 (51.1)
BMI (*M* ± SD)	29.6 ± 6.4	30.0 ± 5.8	28.8 ± 5.1
Diabetes, n (%)	20 (10.2)	55 (20.7)	41 (9.3)
Hypertension, n (%)	12 (6.5)	28 (10.6)	15 (3.6)
Treatment naïve, n (%)	181 (91.9)	256 (96.2)	416 (94.1)
Treatment-experienced, n (%)	16 (8.1)	10 (3.8)	26 (5.9)
Treatment arm			
SOF/DCV, n (%)	108 (54.8)	100 (37.6)	259 (58.6)
SOF/DCV/RBV, n (%)	89 (45.2)	166 (62.4)	183 (41.4)
HCV-RNA $\log_{10}$ (*M* ± SD)	5.6 ± 0.8	5.6 ± 0.9	5.6 ± 0.9
ALT (*M* ± SD)	58.7 ± 43.5	53.6 ± 35.2	58.1 ± 37.9
AST (*M* ± SD)	65.5 ± 39.1	62.2 ± 40.9	63.1 ± 42.0
Albumin (*M* ± SD)	3.9 ± 0.5	3.8 ± 0.6	4.0 ± 0.5
Total bilirubin (*M* ± SD)	0.9 ± 0.4	1.0 ± 0.7	0.9 ± 0.4
WBC (*M* ± SD)	6.0 ± 2.1	5.9 ± 2.3	6.0 ± 2.2
Haemoglobin (*M* ± SD)	13.2 ± 1.8	12.9 ± 1.7	13.2 ± 1.6
Platelets (*M* ± SD)	178.6 ± 71.7	165.0 ± 76.5	176.7 ± 67.1
INR (*M* ± SD)	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.2
Coarse liver echo-texture on ultrasound, n (%)	59 (30.0)	72 (27.1)	106 (24.0)
FIB4, median (IQR)	2.4 (2.8)	2.7 (3.7)	2.2 (2.3)

discontinuations occurred during the first 4 weeks, representing 72.9% of total patients who stopped treatment (Table 7).

4 | DISCUSSION

We report a real-world experience with generic DCV and SOF with or without RBV for treating patient with HCV-G4. This is one of the largest reports presenting real-life data, and of using this combination in treating HCV-G4 patients. Although genotyping was not performed at baseline, more than 90% of patients in Egypt are infected with HCV-G4, and this report can thus be taken to represent results of HCV-G4 treatment.

Optimising treatment outcomes in patients with cirrhosis includes either the addition of RBV or prolonging treatment duration.[28-31] The NCCVH unified treatment duration to 12 weeks and categorised patients to two groups: the so called "easy-to-treat" patients were patients who were treatment naïve, and had no cirrhosis or had normal liver tests. They were treated with SOF-DCV for 12 weeks without RBV. Patients who had previously failed interferon- or SOF-based therapy, patients with cirrhosis, and those who had serum albumin <3.5 g/dL, bilirubin >1.2 mg/dL, INR>1.2 and/or platelet count <150 000/cmm were considered "difficult-to-treat" and were treated with SOF-DCV-RBV for 12 weeks. The assignment criteria resulted in differences between both groups, and in addition, the "difficult to treat" group included a higher proportion of patient with obesity, diabetes and hypertension. Despite these assignment criteria, patients were occasionally assigned incorrectly. That experienced patients assigned by error as "easy-to-treat" (n = 395) responded to treatment without RBV similar to those treated as "difficult-to-treat" suggests that patients who previously failed PEG-RBV or SOF-RBV±PEG are not "difficult-to-treat" using SOF-DCV.

When the NCCVH modified the local guidelines to be based entirely on SOF-DCV or SOF-DCV-RBV combinations, the decision was an economic decision based on the cost of the available local generic medications vs original imported drugs. There were very limited published data on SOF-DCV use in HCV-G4, and efficacy was assumed based on inference from results of SOF-DCV based therapy in HCV-G1 patients. Sulkowski et al recruited HCV-G1, 2 and 3 patients without cirrhosis who were either treatment naïve or experienced. SVR12 ranged between 89%-98% depending on genotype.[8] ALLY-3 and ALLY-3+ studies focused on genotype 3 patients and achieved 86%-92% SVR rates.[17,27] Pol et al reported a real-world experience for 768 HCV-G1 patients, and found an overall 95% SVR12 rate (92-99%), and that the SVR rates were not affected by treatment duration or RBV use.[12] The only local clinical trial using DCV in HCV-G4 patients was in combination with PEG-RBV, and the SVR24 rate in patients treated with DCV 60 mg/day plus PEG-RBV was 100%.[32] The ALLY-1 trial used SOF+DCV in patients with advanced cirrhosis or post-liver-transplantation and included only 4 HCV-G4 patients, who all responded to treatment.[18] Similarly, the ALLY-2 trial treated patients with HCV-HIV coinfection and included

TABLE 6 Multivariate logistic analysis for baseline predictors of non response

	SOF-DCV (n = 10 120)		SOF-DCV-RBV (n = 8258)	
Variable	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Age >60yr.	1.45 (1.12-1.88)	**.01**	1.13 (0.88-1.44)	.35
Male gender	1.25 (1.02-1.54)	**.03**	1.45 (1.18-1.79)	**<.001**
Treatment experienced	0.97 (0.57-1.65)	.91	0.78 (0.53-1.15)	.21
HCV PCR >800,000	1.07 (0.87-1.31)	.54	0.85 (0.68-1.05)	.13
ALT >ULN	1.17 (0.91-1.52)	.23	0.82 (0.63-1.05)	.11
AST >ULN	1.25 (0.96-1.63)	.10	1.44 (1.08-1.93)	**.01**
Albumin <3.5 g/dL	1.52 (1.10-2.10)	**.01**	1.60 (1.29-1.98)	**<.001**
Total bilirubin >ULN	0.93 (0.56-1.54)	.76	1.48 (1.17-1.88)	**<.001**
WBC $<4\times10^3/mm^3$	1.07 (0.77-1.48)	.70	1.16 (0.91-1.49)	.22
Haemoglobin <10 g/dL	1.72 (0.68-4.34)	.25	1.23 (0.48-3.14)	.67
Platelets <150 ($\times10^3/mm^3$)	1.29 (0.92-1.79)	.13	1.57 (1.24-1.97)	**<.001**
Creatinine >ULN	0.57 (0.21-1.55)	.27	2.06 (1.15-3.70)	**.02**
INR>1.2	0.87 (0.57-1.34)	.54	1.29 (1.02-1.63)	**.03**
Coarse liver echo-texture on ultrasound	0.86 (0.64-1.15)	.31	0.92 (0.73-1.15)	.44

TABLE 7 Number and causes of discontinuing therapy (n = 266)

	Number who discontinued therapy	
Reason for discontinuation	**SOF-DCV (n = 100)**	**SOF-DCV-RBV (n = 166)**
Death	0	5
Serious adverse events	6	3
Adverse events	11	24
Decompensation and/or ascites	3	9
Hepatocellular carcinoma	2	3
Acute renal injury	1	3
Hematological	4	5
Ischaemic heart disease	0	2
Hyperbilirubinemia	0	2
Status asthmaticus	1	0
Pregnancy	5	0
Withdrawal	76	136

only 3 patients with HCV-G4, who all responded to treatment.[14] The ANRS-CUPILT report of treating post-liver transplant patients with SOF-DCV in France included 11 patients HCV-G4 patients, and the SVR12 rate was 91%.[20] A real-world report from Europe on compassionate use of SOF-DCV in patients with HCV and advanced liver disease included 19 HCV-G4 patients, and the SVR12 rate was 100% [19]

In this large real-world report of HCV-G4 patients treated with SOF-DCV, the "easy-to-treat" patients achieved 95.4% SVR12 and the "difficult-to-treat" patients including previous treatment failures, patients with cirrhosis, and/or advanced liver disease based on laboratory tests achieved a 94.7% SVR12 rate. We find that using SOF-DCV, with or without RBV, led to a high SVR12 rate among a large group of HCV-G4 patients, under-represented in previous reports. Similar high response rates have been reported with the use of SOF plus DCV with or without RBV from real-life cohorts, even in elderly patients with several concomitant medications (though with much fewer patients).[19,33-35]

Sulkowski et al found that SVR12 rates did not differ after sub analysis of various factors such as sub-genotypes, IL28 phenotype, race, RBV use and history of previous treatment failure with first generation protease inhibitors.[10] Poordad et al found lower albumin levels associated with nonresponse in Child C patients as a reflection of impaired hepatic function.[36] We found several factors that could impact SVR12 rates. These include gender, bilirubin, albumin, INR and platelets.

In this group of patients, only 266 patients (1.45%) prematurely stopped treatment for safety or other reasons, mostly in the group treated with RBV. Treatment was well tolerated: only 0.3% (n = 54) of our patients reported adverse events, serious adverse events, pregnancy and deaths. All previous studies concluded that SOF-DCV combination is safe with limited AEs. High incidence of serious complications (17.5%) was reported by Coilly et al as they managed HCV recurrence in transplanted patients.[20] Such patients are a peculiar situation due to multiple factors that coexist as multi drug intake, immunosuppression and possible drug-drug interactions.

An important factor in this report is the sole use of generic SOF-DCV in all treated patients. Although DAAs provide high cure rates, their high prices could be a barrier to rapid universal treatment uptake.[37-39] Although the price of SOF in the United States was initially set at 84 000 USD for 12 weeks of treatment, Gilead Sciences and the Egyptian NCCVH reached a marked reduced price for the access program in Egypt, at almost 1% of original price (900 USD for 12 weeks' supply of SOF). Gilead Sciences also provided a "voluntary" license agreement to certain manufacturers to produce generic SOF. This allowed low and middle-income countries to obtain generics from these manufacturers. Thus, different Indian generic manufacturers were allowed to produce and sell generic SOF, ledipasvir and velpatasvir in more than 100 countries, including Egypt.[40]

As for DCV, Bristol-Meyers-Squibb signed an agreement with Medicines Patent Pool that authorised sublicensing DCV to many generic manufacturers providing it in 112 countries. This license is somewhat different from the SOF license in the fact that it allows the licensees to market DCV in countries not included in the agreement as long as a patent has not been granted and the manufacturers use alternative manufacturing processes.[41]

As the Egyptian programme for the control and eradication of HCV infection escalated, the need arose for much larger drug production at much lower costs.[35] The MoH strongly supported local producers of generic DAAs by providing "fast track registration" of generic DAAs including SOF and DCV provided they reduced their prices.

Several publications compared the efficacy of brand and generic drugs produced in Egypt[42,43] or used generic SOF with new DAA molecules, such as ravidasvir, that proved safe and effective.[44] Although DAA therapy was found cost-effective at a cost of US$ 40 000 per patient treated in the United States,[45] the initial cost of the generic products used in this report was US$ 240 for a 12-week supply of SOF+DCV. This has since gradually decreased, and at the current exchange rate a 12-week supply to the NCCVH centres costs US$ 84.

Real-world reports are important to highlight the true state of disease management and treatment outcomes in a general patient population and diverse treatment settings. Inclusion and exclusion criteria and patient follow-up are looser than clinical trials, and the much-limited drug-drug interactions in clinical trials cannot be applied in real-world settings. Thus, real-world reports can eventually lead to results that are sub-optimal compared to clinical trials. However, we found in this real-world cohort that efficacy of combined generic SOF-DCV regimen was similar to results of clinical trials. This was associated with good safety results. We can thus recommend this regimen to all HCV-G4 patients with or without cirrhosis who are either treatment naïve or experienced (excluding NS5A experienced patients who were not treated in this cohort).

The major strength of the current report is in the large number of patients included, which is the largest real-world data for the use of SOF-DCV combination in patients with HCV-G4, and the high response rate in patients with different stages of liver disease. However, there are several limitations. The assignment to treatment with RBV was not random and was based on preset baseline criteria, and the treatment groups are not comparable. In addition, fibrosis was not assessed systematically, and assignment to treatment group was based on simplified criteria that could be easily applied in the national program, and patients with cirrhosis and/or ascites were occasionally assigned to treatment with SOF-DCV for 12 weeks without RBV. Another limitation is that the national HCV treatment program in Egypt does not include baseline HCV-genotyping, as more than 90% of HCV infected patients in Egypt are infected with HCV-G4, and the remaining patients are infected with HCV-G1, with genotypes 2, 3, 5 and 6 almost non-existent,[1,2] and this analysis assumes that almost all patients are infected with HCV-G4, and thus the data presented here cannot be generalised to other genotypes.

A further limitation is the absence of a central laboratory for this cohort of patients. All patients treated in the national program are eligible for lab tests at the expense of the state, including baseline, week-4, end-of-treatment, and week-12 post-treatment viral load, which are performed in MoH labs using standard equipment and reagents. However, baseline labs performed elsewhere within the preceding 3 months were accepted, and if patients had their on-treatment or post-treatment tests performed in private labs for convenience, the results were also accepted, and the tests are not repeated. This limitation, however, is a feature of real-life reports, Furthermore, the national program does not perform baseline or at-failure testing for resistance associated substitutions (RAS), and whether baseline presence or development of RASs was responsible for nonresponse or relapse cannot be concluded.

In conclusion, this is a large real-life report of the use of very low-cost generic medications for treating HCV-G4 within the largest treatment programme worldwide. The use of entirely generic SOF-DCV combination with or without generic RBV was well tolerated and associated with high response rate in patients with different stages of liver disease. This can be an example for other countries of similar limited resources for managing their patients with HCV.

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AUTHORSHIP

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Author contributions: Gamal Esmat, Wahid Doss, Yehia El Shazly and Imam Waked planned the study. Mohamed Said, Mohamed El Kassas, Monkez M. Yousif, Ahmed A. Gomaa, Helmy El Shazly, Ahmed M. Nasr, Sohier Ahmed Ismail, Mohamed Kamal Shaker, Kadry Elsaeed and Tamer Elbaz attended patients follow-up visits. Mohamed Abd Allah and Mohamed Korany collected patient data. Wafaa El Akel and Heba Omar did the statistical analysis. Heba Omar, Tamer El Baz and Imam Waked drafted the manuscript, the revisions, and the response to reviewers. All authors contributed equally in manuscript revision and editing. Gamal Esmat and Imam Waked are responsible for the overall content as guarantors. All authors revised and approved the final version of this work.

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