Research Article

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Viral Hepatitis

Sofosbuvir plus ribavirin for treating Egyptian patients with hepatitis C genotype 4

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Background & Aims: Egypt has the highest prevalence of chronic hepatitis C virus (HCV) infection in the world, and more than 90% of patients are infected with genotype 4 virus. We evaluated the efficacy and safety of the HCV polymerase inhibitor sofosbuvir in combination with ribavirin in HCV genotype 4 patients in Egypt.
Methods: Treatment-naïve or treatment-experienced patients with genotype 4 HCV infection (n = 103) were randomly assigned to receive either 12 or 24 weeks of sofosbuvir 400 mg and ribavirin 1000–1200 mg daily. Randomization was stratified by prior treatment experience and by presence or absence of cirrhosis. The primary endpoint was the percentage of patients with HCV RNA <25 IU/ml 12 weeks after therapy (SVR12).
Results: Among all patients, 52% had received prior HCV treatment and 17% had cirrhosis at baseline. SVR12 rates were 90% (46/51) with 24 weeks and 77% (40/52) with 12 weeks of sofosbuvir and ribavirin therapy. Patients with cirrhosis at baseline had lower rates of SVR12 (63% 12 weeks, 78% 24 weeks) than those without cirrhosis (80% 12 weeks, 93% 24 weeks). The most common adverse events were fatigue, headache, insomnia, and anemia. Two patients experienced serious adverse events (cerebral ischemia, dyspnea). No adverse events resulted in treatment discontinuation.
Conclusion: Sofosbuvir plus ribavirin for 12 or 24 weeks is effective in treating both treatment-naïve and treatment-experienced Egyptian patients with genotype 4 HCV.

Keywords: Antiviral agents; Polymerase inhibitor; Hepatitis C; Sofosbuvir; Egypt; Genotype 4.
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Abbreviations: HCV, hepatitis C virus; SVR, sustained virological response; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal; LLOQ, lower limit of quantification; BMI, body mass index.

Introduction

Egypt has the highest prevalence of hepatitis C virus (HCV) infection in the world [1]. The prevalence of HCV viremia was estimated to be 7.3% for the year 2013 [2,3] on the basis of data from the 2008 Egypt Demographic and Health Survey [4]. Egypt also has the greatest number of patients with genotype 4 HCV, more than 90% of those infected or approximately six million people [5]. Within the country, the prevalence of HCV varies among age groups and is highest in persons who received parenteral anti-schistosomiasis treatment in the 1960s–1980s [6]. However, there is evidence that HCV transmission is still occurring at high levels [2]. Given the high prevalence of HCV and its distribution among older generations, Egypt unsurprisingly has the highest burden of advanced liver disease from HCV globally [1].

Until recently, first-line therapy for patients chronically infected with genotype 4 HCV was 24 or 48 weeks of peginterferon-alfa in combination with ribavirin. In patients with genotype 4 infection, rates of sustained virological response with peginterferon and ribavirin treatment are generally higher than seen for genotype 1 HCV but lower than for genotypes 2 or 3 HCV [7]. Given the modest success rates, difficulty of administration, and poor tolerability associated with peginterferon and ribavirin, treatment uptake has been low, and the vast majority of patients with HCV in Egypt are untreated [8].

Sofosbuvir, a potent inhibitor of the HCV NS5B polymerase, has recently been approved for the treatment of HCV in Egypt. Sofosbuvir is administered orally once daily and has a high genetic barrier to resistance. In small cohorts of HCV genotype 4 patients, sofosbuvir in combination with peginterferon and ribavirin has resulted in rates of sustained virological response (SVR) of 82% to 96% [9,10]. Sofosbuvir has a favorable safety profile, and most adverse reactions reported in clinical studies with sofosbuvir have been attributable to concurrent use of peginterferon or ribavirin [11].

A well tolerated, all-oral, interferon-free regimen with a high rate of sustained virological response could have a major impact on the prevalence and incidence of HCV in Egypt. We evaluated the efficacy and safety of 12 or 24 weeks of an all-oral combination of sofosbuvir plus ribavirin in Egyptian patients with HCV genotype 4.

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Patients and methods

Patients

Eligible patients were at least 18 years old and had chronic infection with genotype 4 HCV, with plasma HCV RNA $\geqslant 10^4$ IU/ml. Patients were either HCV treatment naïve or experienced and could have compensated cirrhosis, as determined by the following: biopsy of METAVIR 4 or Ishak $\geqslant 5$, Fibroscan™ >12.5 kPa, or FibroTest™ >0.75 and AST:platelet ratio index >2. Patients with any of the following conditions or characteristics were excluded from participation: BMI <18 kg/m^2; decompensated liver disease; chronic use of systemically administered immunosuppressive agents, such as prednisone equivalent >10 mg/day; HIV infection; hepatitis B virus infection; creatinine clearance <60 ml/min as calculated by the Cockcroft-Gault equation; hemoglobin <11 g/dl for females and <12 g/dl for males; platelets $\leqslant$50,000/mm^3; direct bilirubin $\geqslant 1.5 \times$ ULN; alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase >10 $\times$ ULN; hemoglobin A1c >10%; chronic liver disease of a non-HCV etiology; contraindication to ribavirin therapy; history of malignancy diagnosed or treated within the prior five years; or excessive alcohol ingestion, defined as >3 glasses/day. All patients provided written informed consent before undertaking any study–related procedures.

Study design

This was a multi-center, open-label study. Patients were randomly assigned 1:1 to receive 12 or 24 weeks of sofosbuvir 400 mg and ribavirin 1000–1200 mg orally every day. Treatment assignments were stratified on the basis of prior treatment experience and the presence or absence of cirrhosis. Up to approximately 20% of patients were allowed to have compensated cirrhosis at screening. After treatment, patients underwent follow-up for up to 24 weeks.

Treatment was to be stopped for patients with the following virologic criteria: confirmed HCV RNA $\geqslant$ the lower limit of quantification (LLOQ) after two consecutive HCV RNA <LLOQ, confirmed HCV RNA >1 $\log_{10}$ increase from nadir, or HCV RNA $\geqslant$LLOQ through eight weeks of treatment.

The study protocol was approved by each institution's review board prior to study initiation. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization guidelines.

Efficacy assessments

Plasma samples for determining HCV RNA levels were drawn at screening; on day one of treatment; at weeks 1, 2, 4, 6, 8, 10, 12 of treatment for all patients plus weeks 16, 20, and 24 weeks for patients receiving 24 weeks of treatment; and at follow-up weeks 4, 12, and 24. Plasma HCV RNA was analyzed by using the Roche COBAS TaqMan HCV Test, v2.0 for use with the High Pure System (Roche Molecular Systems, Inc., Branchburg, NJ), which has a LLOQ of 25 IU/ml.

Viral sequencing

Plasma samples for viral sequencing were collected at the same time points as for HCV RNA levels. For all patients who did not achieve SVR12, deep sequencing of the HCV NS5B-encoding region of the viral polymerase, with a 1% assay cut-off, was performed at baseline and the first virologic failure time point for viral samples if HCV RNA $\geqslant$1000 IU/ml. The HCV NS5B coding regions were amplified and population or deep sequenced by DDL Diagnostic Laboratory (Rijswijk, The Netherlands) using standard reverse transcription polymerase chain reaction technology. Amino-acid substitutions in the NS5B in the samples collected at virologic failure were compared with the respective baseline sequence for each patient. The availability of short fragment population sequence of the NS5B coding region from subtype determination allowed for baseline characterization of the S282 residue from all patients that achieved SVR12. NS5B nucleoside inhibitor (NI) RAVs were defined as the following substitutions at the following positions: S96T, N142T, L159F, S282 any, M289I/L/V, L320F, and V321A.

Safety assessments

Safety data was collected during treatment and for up to 30 days after the last dose of study drug. The data included reported adverse events, physical examinations, clinical laboratory tests, vital signs, and ECG recordings. Concomitant medication intake was also recorded. Treatment–emergent clinical and laboratory adverse events were summarized using the Medical Dictionary for Regulatory Activities (MedDRA®), version 17.0.

Endpoints and statistical analyses

The primary efficacy endpoint was the percentage of patients in each study group with SVR12, defined as HCV RNA <LLOQ (25 IU/ml) 12 weeks after stopping study drug. No inferential statistics or statistical comparisons were planned for efficacy endpoints. Along with the percentage of patients with SVR12, for each treatment group a two-sided 95% confidence interval was constructed by using the exact binomial distribution. With a sample size of 50 subjects in each arm, a two-sided 95% exact confidence interval was estimated to extend at most 29% in length.

Results

Study population

From March 2013 through August 2014, 103 patients were enrolled and treated at three sites in Egypt. A majority (67%) of patients were male (Table 1) and 52% had received prior HCV treatment. In all, 17% had cirrhosis at baseline; cirrhosis was determined on the basis of Fibroscan testing in the majority of patients. Mean HCV RNA levels were similar between the two treatment groups. All patients except one completed study treatment (Fig. 1). That patient, in the 24-week group, was lost to follow-up.

Antiviral response

By week four of therapy with sofosbuvir and ribavirin, all patients had HCV RNA <LLOQ, and all maintained virological suppression while receiving therapy. The percentage of patients achieving SVR12 was higher in the group receiving 24 (90%) *vs.* 12 (77%) weeks of sofosbuvir and ribavirin therapy (proportional difference [95% confidence interval], −13.3% [−28.5% to 1.4%]) (Table 2). In both treatment groups, patients with cirrhosis at baseline had lower rates of SVR12 (63% 12 weeks, 78% 24 weeks) than those without cirrhosis (80% 12 weeks, 93% 24 weeks). In the group receiving 12 weeks of sofosbuvir and ribavirin, HCV treatment naïve patients had a higher rate of SVR12 (84%) than patients who received prior treatment (70%). All patients in both treatment groups with *IL-28B* genotype CC (n = 20) achieved SVR12. For non-CC genotypes, the SVR12 rate was higher among patients receiving 24 weeks (88%, 35/40) than 12 weeks (72%, 31/43). All virologic failures were due to relapse; 14 patients who relapsed after completing a full regimen of therapy had detectable HCV RNA by week four of follow-up and two additional patients who received 12 weeks of treatment had detectable HCV RNA at Week 12 post-treatment. One patient was lost-to-follow-up and classified as a treatment failure in the efficacy analysis. All patients who achieved SVR12 had HCV RNA <LLOQ at 24 weeks post therapy (SVR24).

Viral sequencing

Viral isolates from 102 of 103 patients enrolled had successful baseline sequencing performed of the region covering the sofosbuvir resistance-associated variant site S282. No variants in this region were observed at baseline in the 87 patients with population sequencing for this region or in the 15 with full NS5B deep sequencing data. No S282T variants were observed at the virologic failure time points in the patients who did not achieve SVR12 (15 deep sequencing and one population sequencing).

Table 1. Patient demographics and baseline characteristics.

	Sofosbuvir + ribavirin 12 weeks n = 52	Sofosbuvir + ribavirin 24 weeks n = 51
Mean (SD) age, yr	45 (11.9)	49 (11.7)
Male, n (%)	37 (71)	32 (63)
Race, n (%)		
White	52 (100)	51 (100)
BMI <30 kg/m^2, n (%)	28 (54)	26 (51)
Genotype 4 subtype, n (%)		
4a	44 (85)	46 (90)
4l	1 (2)	0
4n	2 (4)	2 (4)
4o	4 (8)	1 (2)
4p	0	1 (2)
4u	0	1 (2)
Not determined	1 (2)	0
Mean (SD) HCV RNA, $\log_{10}$ IU/ml	5.8 (0.66)	5.9 (0.74)
IL-28B, n (%)		
CC	9 (17)	11 (22)
CT	30 (58)	33 (65)
TT	13 (25)	7 (14)
Cirrhosis, n (%)		
Present	8 (15)	9 (18)
Method of cirrhosis detection, n (%)		
Biopsy	4 (8)	6 (12)
Fibroscan	38 (73)	38 (74)
Fibrotest + APRI score	10 (19)	7 (14)
Platelets <100 x 10^3/L, n (%)	3 (6)	0
Albumin <3.5 g/dl, n (%)	2 (4)	2 (4)
Prior HCV treatment	27 (52)	27 (53)
Non-response, n	12	10
Breakthrough, n	15	17
Prior schistosomiasis infection, n (%)		
Never infected	26 (50)	28 (55)
Previously infected	14 (27)	19 (37)
Unknown	12 (23)	4 (8)

APRI, aspartate aminotransferase to platelets ratio; BMI, body mass index; HCV, hepatitis C virus.

No other sofosbuvir treatment-emergent variants were observed in the 15 samples successfully deep sequenced at baseline or the 15 samples successfully sequenced at failure time points.

Safety assessments

No patients discontinued treatment due to adverse events (Table 3). Two patients, both receiving 24 weeks of sofosbuvir and ribavirin, were reported as having a serious adverse event. One had dyspnea, which was considered treatment related, and the other had cerebral ischemia, which was not considered related to treatment.

Consistent with ribavirin dosing, the most common adverse event was fatigue. Sixteen patients (six in the 12 week group and ten in the 24 week group) had treatment-related anemia,

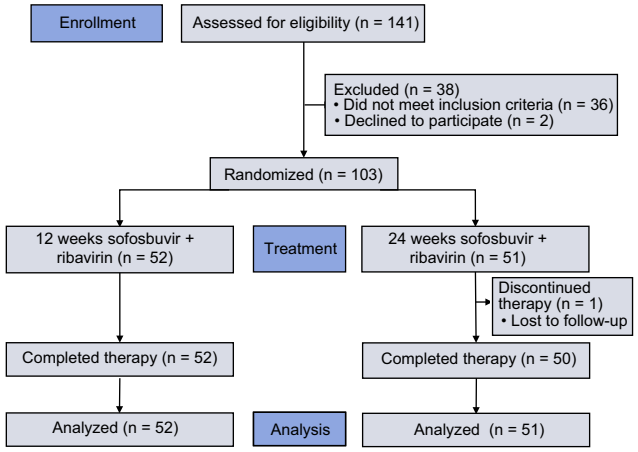

Fig. 1. Patient disposition throughout the study.

and 14 patients (four in the 12 week group and ten in the 24 week group) had hemoglobin levels drop below 10 g/dl. Only one patient, receiving 24 weeks of therapy, had hemoglobin levels drop below 8.5 g/dl. Thirteen patients (four in the12 week group and nine in the 24 week group) had a ribavirin dose reduction in response to having anemia or decreased hemoglobin. No patients received erythropoietin for managing anemia.

Discussion

Based on data from the 2008 Egypt Demographic Health Survey, approximately six million persons in Egypt were estimated to HCV viremia in 2013 [2,3]. The vast majority of infected patients have not received treatment [1]. The origin of the HCV epidemic in Egypt has been attributed to unsafe injection practices during a campaign of parental anti-schistosomiasis treatment of children and young adults in the 1960s–1980s [12]. Persons infected during this time comprise an aging cohort of HCV-positive individuals becoming increasingly at risk for advanced liver disease. Transmission of HCV infection continues to occur, primarily through medical exposures. Egypt currently has the highest burden of advanced liver disease from HCV globally, and estimates suggest that in Egypt in 2013 there were 770,000 persons with cirrhosis, 16,000 HCV-related HCC cases, and 33,000 HCV-related liver deaths.

Given the scale of the HCV epidemic in Egypt, a treatment regimen that is simple and of short duration is critical for treatment uptake to be widespread and successful. The results of this study suggest an interferon-free regimen of sofosbuvir and ribavirin 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 (90%) *vs.* 12 (77%) weeks of therapy. The presence of cirrhosis was associated with lower rates of SVR12 in both the 12- and 24-week groups. Undergoing 24 *vs.* 12 weeks of treatment appears to have some benefit, especially for patients who are treatment-experienced or who have cirrhosis. However, given the limited number of treatment-experienced patients with cirrhosis included in this study, no definitive conclusions may be drawn regarding the safety and efficacy of sofosbuvir plus ribavirin for 24 weeks in this population. Further evaluation of this and other treatment options in larger studies is warranted.

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Table 2. Virological response.

	Sofosbuvir + ribavirin 12 weeks n = 52	Sofosbuvir + ribavirin 24 weeks n = 51
SVR12, no./total no. (%)		
All patients	40/52 (77)[a]	46/51 (90)[a]
No cirrhosis	35/44 (80)	39/42 (93)
Cirrhosis	5/8 (63)	7/9 (78)
HCV treatment naive	21/25 (84)	22/24 (92)
No cirrhosis	19/22 (86)	19/21 (90)
Cirrhosis	2/3 (67)	3/3 (100)
HCV treatment experienced	19/27 (70)	24/27 (89)
No cirrhosis	16/22 (73)	20/21 (95)
Cirrhosis	3/5 (60)	4/6 (67)
Virologic failure, no./total no. (%)		
All patients		
On treatment	0	0
Relapse	12/52 (23)	4/51 (8)
HCV treatment naive		
Relapse	4/25 (16)	1/24 (4)
HCV treatment experienced		
Relapse	8/27 (30)	3/27 (11)

HCV, hepatitis C virus; SVR12, sustained virological response, defined as hepatitis C virus RNA <25 IU/ml 12 weeks after cessation of therapy.
[a]The proportional difference (95% CI) in SVR12 percentages between 24 and 12 weeks was −13.3% (−28.5% to 1.4%).

Table 3. Treatment-emergent adverse events and laboratory abnormalities.

	Sofosbuvir + ribavirin 12 weeks n = 52	Sofosbuvir + ribavirin 24 weeks n = 51
No. (%) of patients with any adverse event	39 (75)	42 (80)
No. (%) of patients with a serious adverse event	0	2 (4)
Adverse event leading to discontinuation, n	0	0
Deaths, n	0	0
Adverse events ≥10% of patients, n (%)		
Fatigue	7 (13)	14 (27)
Headache	6 (12)	11 (22)
Insomnia	7 (13)	10 (20)
Anemia	6 (12)	10 (20)
Dyspepsia	4 (8)	8 (16)
Pruritus	2 (4)	9 (18)
Oropharyngeal pain	3 (6)	6 (12)
Upper abdominal pain	6 (12)	3 (6)
Serious adverse events, n (%)		
Cerebral ischemia	0	1 (2)
Dyspnea	0	1 (2)
Laboratory abnormalities		
Serum glucose (250 to 500 mg/dl)	1 (2)	2 (4)
Total bilirubin (>2.5 to 5 x ULN)	2 (4)	0
Lipase (<5 x ULN)	1 (2)	0
Hemoglobin (<8.5 g/dl)	0	1 (2)
Neutrophils (<0.75 x 10^3/μl)	0	1 (2)

The results in this study are consistent with those in a phase two study evaluating treatment with sofosbuvir plus ribavirin for 12 or 24 weeks in patients of Egyptian origin with genotype 4 HCV infection [13]. SVR12 rates were 68% (21/31) following 12 weeks of treatment and 93% (27/29) following 24 weeks of treatment. Although only a small number of patients had cirrhosis, 43% (3/7) receiving 12 weeks of treatment and 100% (7/7) receiving 24 weeks achieved SVR12. In this study, as in the Ruane *et al.* [13] study, successful response to therapy was durable: of patients reaching SVR12, 100% reached SVR24. In this study, the combination of sofosbuvir and ribavirin was generally well tolerated, and adverse events were consistent with ribavirin dosing.

Other direct-acting antivirals also have been or are currently being studied for the treatment of genotype 4 HCV infection. Simeprevir in combination with peginterferon and ribavirin, with a total treatment duration of 24 to 48 weeks, resulted in SVR12 rates of 83% (29/35) in treatment-naïve and 57% (41/72) in treatment-experienced patients [14]. Regimens containing an NS5A inhibitor, such as daclatasvir, ombitasvir, or ledipasvir, have reported particularly high rates of SVR12 in patients with genotype 4 HCV. In a phase two study [15], daclatasvir in combination with peginterferon and ribavirin for 24 weeks resulted in a 100% SVR12 rate in a group of 12 treatment-naïve patients. In a randomized phase 3 study of treatment-naïve patients [16], 67 of 82 (82%) patients receiving daclatasvir plus peginterferon-ribavirin had SVR12 compared with only 18 of 42 (43%) patients receiving peginterferon-ribavirin. In a study of 44 genotype 4 HCV patients who failed prior treatment, 100% achieved SVR12 after 24 weeks of daclatasvir plus asunaprevir with peginterferon and ribavirin [17]. An all-oral regimen of daclatasvir plus beclabuvir and asunaprevir for 12 weeks resulted in a 100% SVR rate in 21 treatment-naïve patients with genotype 4 HCV [18]. Ombitasvir plus paritaprevir plus ritonavir with and without ribavirin was evaluated in a phase 2 study in treatment-naïve and treatment-experienced patients with genotype 4 HCV [19]. SVR12 rates were 91% (40/44) in treatment-naïve patients who received the regimen without ribavirin and 100% in both treatment-naïve (42/42) and treatment-experienced (49/49) patients who received the ribavirin-containing regimen. Ledipasvir in a fixed dose combination with sofosbuvir for 12 weeks was evaluated in 21 treatment-naïve and treatment-experienced patients with HCV genotype 4 infection; 19 of 20 (95%) patients who had reached 12 weeks post-treatment at the time of analysis achieved SVR12 [20].

Worldwide, genotype 4 accounts for only 13% of HCV infections [5]; however, there are several countries in the Middle East and Sub-Saharan Africa where it accounts for more than half of infections [5]. Thus, the results of this study could have broader implications beyond the Egyptian population.

The main limitation of this study is its sample size, which makes subgroup comparisons difficult.

In summary, treatment with the all-oral regimen of sofosbuvir and ribavirin resulted in a high rate of SVR among patients with genotype 4 HCV in Egypt. This country, which is experiencing an epidemic of HCV, may benefit from the availability of an all-oral therapy.

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Conflict of interest

G.E. Esmat is a consultant to Gilead, AbbVie, BMS, GSK, Janssen, MSD, Roche. G. Shiha, R.F. Omar, M. Hassany, R. Hammad, M. Khairy, W. Samir, R. Soliman, and W.H. Doss have nothing to disclose. The following authors are employees of Gilead Sciences and may hold stock interest in the company: Brian Doehle, Deyuan Jiang, Kathryn Kersey, Steven J. Knox, Benedetta Massetto, and John G. McHutchison.

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