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Safety and efficacy of combination therapy (Simeprevir/Sofosbuvir) in the treatment of chronic HCV genotype IV patients

Engy A. Wahsh[1], Amal K. Hussein[2], Ahmed A. Gomaa[3], Mohamed A. Baraka[4,5], Mohie Al-deen Abead[6]

[1]Nahda University, Faculty of Pharmacy, Department, Clinical Pharmacy, Beni Suef, Egypt
[2]Minia University, Faculty of Pharmacy, Department of Pharmaceutical Technology, Minia, Egypt
[3]Fayoum University, Faculty of Medicine, Department, Tropical Medicine, Fayoum, Egypt
[4]Al-Azhar University, Faculty of Pharmacy, Department of Clinical, Pharmacy, Egypt
[5]University of Dammam, College of Clinical Pharmacy, Department of Pharmacy Practice, Saudi Arabia
[6]Ministry of Interior, Ph.D Biochemistry, Egypt

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Abstract

Chronic infection with HCV is a worldwide health problem that may lead to cirrhosis, portal hypertension, hepatocellular failure and hepatocellular carcinoma in most of cases. A new era in HCV treatment has been started using direct acting antiviral activity. In this study we assess the safety and efficacy of a combination therapy Sofosbuvir/Simprevir in the treatment of chronic HCV patients genotype IV either cirrhotic or non-cirrhotic. In the outpatient clinic, one hundred and seventy five chronic HCV patients were recruited from Tropical Medicine Department at Fayoum public hospital. A combination of Sofosbuvir (400 mg) and Simeprevir (150 mg) was administered for those patients once daily over a period of 12 weeks. All patients have been followed up for clinical and laboratory parameters and HCV PCR to evaluate the efficacy and safety of this therapy. Sustained Virologic Response rate (SVR12) were 97.7% (169/173) (primary end point), and same results obtained at the second end point (SVR 24). In this study, cirrhotic patients showed lower SVR (92.7%) compared to non-cirrhotic patients (98.5%) (p-value 0.085). Majority of patients (57.14%) reported adverse events (AEs) during treatment and most common AEs were headache, fatigue, pruritus, dizziness and photosensitivity. On the basis of the evidence currently available, it seems fair to suggest that the combination therapy of (SMV/SOF) in the treatment of chronic HCV genotype IV naïve and experienced patient whether cirrhotic or non-cirrhotic is safe and effective. This was evidenced by monitoring patients' clinically and using hepatic parameters after drug administration. The adverse events affected patients were mild and tolerable among patients.

Keywords: Chronic hepatitis C, genotype IV, simeprevir, sofosbuvir

Introduction

Hepatitis C virus infection (HCV) remains an evolving cause of morbidity and mortality worldwide [1]. The World Health Organization (WHO) declared that HCV affects about 3% of the world's population, and more than 170 million patients are chronic, around 3–4 million persons are recently infected patients [2] and 350000–500000 HCV-related deaths are reported annually [3]. HCV has been undergoing global spread for over 100 years [4].

Chronic infection with HCV is a global health problem which may lead to cirrhosis, portal hypertension, hepatocellular failure and hepatocellular carcinoma, making HCV an important cause of liver transplantation [5]. It was reported in previous studies that 80% of Patients recently infected with HCV turn into chronic, 10%–20% of them develop cirrhosis and 1%–5% progress to hepatocellular carcinoma and other liver complications over a period of 20–30 years [2].

Prevalence of HCV infection vary widely and ranges from the lowest (0.15%) found in Scandinavia to the highest (15%) in Egypt [2]. Egypt has the highest prevalence of HCV infection worldwide; about 9% of the total population and up to 50% in certain rural areas in the country [1]. A major problem is that one half to three quarters of persons currently infected with HCV have not received a diagnosis and are untreated. It has been documented that early diagnosis and treatment are essential to improve long-term health outcomes in this population [6]. The goal of HCV therapies is to minimize the high morbidity and mortality associated with the chronic infection with HCV [7].

HCV is classified into six major genotypes, each distributed in specific region all over the world [8]. The differences of HCV

***Coresponding Author:** Engy Wahsh, Nahda University, Faculty of Pharmacy, Department, Clinical Pharmacy, Beni Suef, Egypt
E mail: engy_wahsh@yahoo.com

genotypes have a great clinical value as they affect responses to antiviral therapy. The most prevalent (approximately 90%) one in Egypt is genotype [4]. A closer relationship exists between genotype 4 and genotype 1 than with other genotypes has been confirmed after Phylogenetic analysis of the complete genomic sequence of genotype 4. This has been presented by the short branch and the large degree of similarity in nucleotide sequence between genotypes 1 and 4 than that found between other genotypes [9].

The most commonly used therapy in Egypt for chronic HCV before discovery of direct-acting antiviral drugs was pegylated-interferon alfa (PEG-IFN) administered with ribavirin, with efficacy demonstrated as a sustained virological response (SVR) more than 60% of patients after 48 weeks of therapy. Different side effects were reported during treatment with PEG-IFN including fever, headache, fatigue, bone aches, neuropsychiatric symptoms and bone marrow suppression. Addition of ribavirin to the regimen lead to other side effects as hemolytic anemia, dyspnea and cutaneous complications [10] .

A new era in HCV treatment has begun after deep realizing of the genome and the life cycle of HCV. This allowed for the discovery of new therapy targets that directly inhibit replication [7]. Some of These drugs improve the SVR up to 100% and have fewer side effects with shorter duration of therapy. At the end of 2013, the Food and Drug Administration (FDA) approved two new direct-acting antiviral (DAA) agents for the treatment of HCV infection: namely Sofosbuvir (SOF) which is a non-structural protein 5B (NS5B) polymerase inhibitor and the second-generation the non-structural 3/4A (NS3/4A) protease inhibitor simeprevir (SMV) [11]. Quite recently, considerable attention has been paid to such therapies and their impact on HCV management. The aim of our study is to assess the safety and efficacy of combination therapy Sofosbuvir/Simprevir in the treatment of chronic HCV patients, genotype IV either cirrhotic or non-cirrhotic.

Material and Methods

One hundred and seventy five chronic HCV patients were recruited from the outpatient clinic at Tropical Medicine Department, Fayoum public hospital, from April 2015 to August 2016, with a follow-up period of 36 weeks, according to the following inclusion and exclusion criteria

Inclusion Criteria

Adult Egyptian male and female patients aged 18 – 70 years with no specification on body mass index (BMI), who have Detectable serum quantitative HCV RNA and who are Treatment naïve or treatment experienced with all fibrosis stages. Assessment of fibrosis is no longer necessary and performing liver biopsy or transient elastography (fibroscan) is not a pre-requisite; however, collection of such data is encouraged if available at the time of presentation.

Exclusion criteria: any of the following,

- Patients with Direct serum bilirubin >2 mg/dl.
- Serum albumin <2.8 g/dl.
- INR ≥ 1.7
- Platelet count < 50000/mm3
- Hepatocellular carcinoma (HCC), except 4 weeks after intervention aiming at cure with no evidence of activity by dynamic imaging (CT or MRI).
- Serum creatinine >2.5 mg/dL. If creatinine is between 1.5 and 2.5 mg/dL, eGFR should be calculated and should exceed 30 mL/min with favorable nephrological consultation.
- Extra-hepatic malignancy except after two years of disease-free interval.
- Co-infection with hepatitis B virus or HIV
- Pregnancy or inability to use effective contraception
- Organ transplant.

Study design

The study was conducted on treatment naïve and treatment experienced patients with chronic HCV genotype 4 with cirrhotics and non-cirrhotic liver. Cirrhosis was diagnosed on ultrasound basis and laboratory investigation. All patients received Sofosbuvir 400 mg and simeprevir 150 mg (SMV/SOF) once daily for 12 weeks. All patients have been followed up after receiving the therapy and data was collected about the following parameters with the purpose of comparing the changes before and after receiving the combination therapy: Full clinical examination and history taking information were also recorded.

1. Laboratory investigations include:

- Complete blood count
- Complete biochemical profile: aspartate amino transferase (AST), alanine amino transferase (ALT), serum albumin, serum creatinine, total bilirubin, prothrombin concentration and international normalized ratio (INR).
- Serum alpha-fetoprotein (AFP) was also measured before treatment (if > 100 triphasic CT abdomen should be done to exclude HCC).
- Thyroid function test
- Random blood sugar

2.Fundus examination and ECG

3.Follow up for clinical, laboratory assessment and HCV PCR for the purpose of documenting the patients' response (efficacy) and side effects (safety) of treatment.

The end point was defined as (SVR) of less than 15 IU per milliliter at 12 weeks (SVR 12) and 24 weeks(SVR 24) of treatment determined by quantitative PCR for HCV.

Statistical Analyses

Descriptive analysis has been performed and frequency and percentage of all variables' categories have been tabulated. For continuous data, the mean and standard deviation (Mean ± SD) have been reported. Statistical associations between pairs of categorical variables were assessed using $\chi 2$-tests. Changes in the measured laboratory parameters before and three months after the treatment have been examined using dependent student-t test to determine whether improvement or deterioration in laboratory investigations has been observed. P-values less than 0.05 were considered as significant results. All statistical analyses were performed using IBM-SPSS version 22.0 (SPSS, Chicago, IL, USA).

Results

The baseline demographic and clinical characteristics of patients were presented in table 1. Out of 175 study participants, there were 148 naïve patients (35 cirrhotic patients) and 27 experienced (6 cirrhotic patients). All patients received SMV/SOF combination therapy for treatment of chronic HCV. Baseline characteristics

revealed that 76% were males (133 of 175). Cirrhotic patients presented (23.43%) of the population treated.

Table 1. Patient Demographics and Baseline Characteristics (n=175)

Title	M± SD ; N (%)
Age (years)	52.4 ±11.9
0-40	27 (15.43%)
40-60	80 (45.71%)
60-75	68 (38.86%)
Gender	
Male	133 (76 %)
Female	42 (24%)
BMI	29.97 ± 5.68
Comorbidities	
DM	43 (24.6 %)
HTN	30 (17.1 %)
Smokers	19 (10.9 %)
ANA positive	3 (1.7 %)
HBsAg positive	0
HCV Treatment history	
Naïve	148 (84.6%)
Experienced	27 (15.4%)
Liver cirrhosis	41 (23.4%)

As shown in table 2, the laboratory data for all patients receiving therapy were recorded before treatment and three months later. Mean improvements in laboratory values after 3 months of treatment were also observed for albumin and alpha fetoprotein. On the other hand there is no significant difference for total bilirubin, WBC, HGB, platelets and creatinine before and after treatment. The data presented in table 2 demonstrated a significant decline in liver enzymes mean values after beginning of treatment. The mean of AST values before treatment was 51.7 IU, while after 1 month it has been reduced to 23.76 IU and further declined to 22.76 at the end of treatment. The mean of ALT values before treatment was 53.25 IU while after 1 month, it has declined significantly to21.8 IU and at the end of treatment it was 21.01 IU.

Table 2. Laboratory data for patients

	Before ttt (175)	3 months(174)	
HCV RNA (IU) log 10	5.68 ± 0.82	1.18 ± 0.00	<0.001
ALT (IU/L) (ULN: 4 0 IU/L)	53.25 ±33.60	21.01±8.22	<0.001
AST (IU/L) (ULN: 40 IU/L)	51.70 ±34.16	22.76 ±8.53	<0.001
AFP (IU/L) (ULN: 10 IU/L)	13.74 ±29.75	10.91 ±24.10	0.001
Albumin (g/dL)	4.01 ± 0.54	4.07 ± 0.54	0.021
Total Bilirubin (mg/dL)	0.86 ± 0.50	0.87 ± 0.52	0.682
WBC×103/mm3	6.20 ± 2.12	6.45±2.03	0.205
Platelets × 103/mm3	182.2 ± 75.2	185.4 ± 71.6	0.129
HGB (G/L)	13.50 ± 1.74	13.50 ± 1.71	0.503
*PC (%)	85.90 ± 14.69		
*INR	1.13 ± 0.17		
Creatinine (mg/dL)	0.89 ± 0.26	0.90 ± 0.29	0.422
Glucose (mg/dL)	104.89±30.83	109.07±46.15	0.066
*TSH	2.94 ± 14.93		

* values measured at beginning of treatment only

The results show that a rapid serum HCV RNA decline was observed with 97.1% of patients (170/175) below detection limits at treatment week 4. This has been further emphasized at the end of therapy where the PCR was negative in 100% of the patients. Sustained Virologic Response rate (SVR12) in this study population was 97.7% (169/173) (primary end point), and the same reached at second end point (SVR 24). The characteristics of patient failed to receive SVR12 presented in table 3. In this study, cirrhotic patients showed lower SVR (92.7%) when compared to non-cirrhotic populations (98.5%;p value 0.085).

Table 3. Characteristics of patient failed to receive SVR12

Title	M± SD ; N (%)
Age (years)	53.5 ± 12.3
Gender (male)	4 (100%)
DM	0
HTN	1(25%)
Smokers	1 (25%)
ANA positive	0
HBsAg positive	0
HCV Treatment history (Naïve)	3 (75%)
Liver cirrhosis	2 (50%)
Ascites	0
HCV RNA (IU) log 10	5.93 ± 0.76
ALT (IU/L) (ULN: 4 0 IU/L)	57.75 ± 23.98
AST (IU/L) (ULN: 40 IU/L)	67 ± 25.97
AFP (IU/L) (ULN: 10 IU/L)	47.22 ± 54.15
Albumin (g/dL)	3.55 ± 0.44
Total Bilirubin (mg/dL)	1.2 ± 0.68
WBC×103/mm3	4.85 ± 0.83
Platelets × 103/mm3	143.75 ± 79.19
HGB (G/L)	13.82 ± 1.35
PC (%)	74.75 ± 17
INR	1.24 ± 0.19
Creatinine (mg/dL)	0.85 ± 0.09
Glucose (mg/dL)	92.75 ± 13.05
TSH	1.6 ± 1.74

According to results shown in table 4, 100 (57.14%) patients reported adverse events (AEs) during treatment; most AEs were grade 1 or 2 (65%). Only one patient discontinued treatment due to severe rash and pruritus. The most common AEs reported were headache, fatigue, pruritus, dizziness and photosensitivity. Serious AEs were reported by one patients and another patient died after 3 months of treatment. Increased bilirubin was reported as an AE by 17 (9.7%) patients. All rash or photosensitivity AEs were mild to moderate except for one who stops treatment.

The results show that there was a slightly significant increase in glucose level for diabetic patients using oral hypoglycemic and only 2 patients from insulin dependent patients needed to increase insulin dose. These findings were demonstrated in table 5.

Table 4. Summary of adverse events and laboratory abnormalities

Title	N (%)
No. (%) of patients with any adverse event, n	100 (57.14 %)
No. (%) of patients with a serious adverse event	1 (0.6%)
Adverse event leading to discontinuation	1 (0.6 %)
n (%) Deaths	1 (0.6 %)
Fatigue	22 (12.6 %)
Photosensitivity	11 (6.3 %)
Headache	29 (16.6 %)
Pruritis	11 (6.3 %)
Dizziness	9 (5.1 %)
Arthralgia	7 (3.4%)
Hypertension	1 (0.6%)
Fever	2 (1.1%)
Leg swelling	3 (1.7%)
Nausea	2 (1.1%)
Bilirubin increase >1.2	17 (9.71%)

Table 5. The effect of therapy in glucose level for different types of patient

	Non diabetic patients	Diabetic patient who are Insulin dependent	Diabetic patient on oral hypoglycemic
No.	132	20	23
Mean glucose level±SD before ttt	95.1± 14.9	140.1± 50.8	131.4± 38.8
Mean glucose level±SD after ttt	96.4± 23.3	137.4± 45.2	160± 57.9
p-value	0.277	0.783	0.065

Discussion

The purpose of this study is to assess the safety and efficacy of simeprevir plus sofosbuvir in treatment of HCV naïve and experienced patients regardless being cirrhotic or non-cirrhotic. Our observations that the serum HCV RNA and SVR declined significantly after 4 weeks of therapy and were absent in all patients after 12 weeks give us an indication about the efficacy of this combination therapy in managing HCV patients. However, the overall SVR12 among cirrhotic patients was lower than that observed among non-cirrhotic patients, while statistical significance in that difference could not be achieved.

These results obtained from our study are broadly consistent with the major trends of proven efficacy of such combination therapy in managing HCV as shown in several previous publications [12-20]. Our findings were matching with the published results of a Phase III (PLUTO) clinical trial which investigated Simeprevir in combination with sofosbuvir in treatment of naïve and experienced patients with and without compensated cirrhosis in hepatitis C virus genotype 4 infection where this combination achieved SVR rate of 100% among study subjects [12]. Our results concur also with the OSIRIS study, where the SVR12 rate attained was also 100% for patients with and without cirrhosis who received the same combination for 12 weeks [13].

This study results are also consistent with a recent study conducted in 2016 by Eletreby et al. Their study revealed that The SVR12 rate achieved among a cohort of 6211 patients with genotype 4 HCV infection was 94.0% while the end of treatment response rate was 97.6%. Their study reported a SVR in easy and difficult- to-treat groups were 96% and 93% respectively after 12 weeks [14].

The results of this study are in good agreement with other study conducted by El- khayat et al., 2016 who assessed SVR 12 for 583 Egyptian patients with HCV genotype 4 infection after receiving SIM/SOF without ribavirin for 12 weeks. Overall SVR12 rate in their study was (95.7%), and was lower among cirrhotic patients (80.8%) [15].

Similar results have also been reported by Moreno et al., 2015 with 100% SVR12 of HCV genotype 4-infected patients with cirrhosis, treated with or without ribavirin [16] The results of this study is complemented by Phase III OPTIMIST-1 study in HCV genotype 1-infected patients without cirrhosis treated with simeprevir plus sofosbuvir for 12 weeks achieved 97% SVR12 [17], while in Phase III OPTIMIST-2 study in patients with cirrhosis achieved 83% SVR12 [18].

The target SVR12 achieved in our study was higher than that achieved by Flamm et al., 2014 who studied the effect of Ledipasvir (NS5A inhibitor) plus sofosbuvir for treating HCV-4 infected patients [19]. Patients achieved SVR12 of 87% when RBV was added to this combination for 12 weeks in HCV genotype 1 and 4 infected patients with decompensated cirrhosis [19]. In contrast to our findings, a higher SVR12 rate was reported in other study in which HCV-1 infected patients treated with sofosbuvir and ledipasvir for 12 weeks have achieved 97% and 99% SVR12 with and without ribavirin respectively [20].

The combination therapy we studied here resulted also in improvements in liver enzymes and other parameters' readings, such as albumin and alpha-fetoprotein after 3 months of drug therapy.

We have addressed not only the efficacy of this combination therapy, but also considered other consequences of these drugs exposure in terms of safety. This combination therapy appeared to have a mild to moderate symptoms of rash, photosensitivity, headache, fatigue and dizziness that does not outweigh its benefits for HCV patients.

Conclusions

From the research that has been conducted, it is possible to conclude that combination therapy of (SMV/SOF) in the treatment of chronic HCV genotype IV naïve and experienced patient whether cirrhotic or non-cirrhotic is safe and effective. This was evidenced by monitoring patients' clinically and using hepatic parameters after drug administration. The adverse events affected patients were mild and tolerable among patients.

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Authors' contributions

Amal K. Hussein, Ahmed A. Gomaa contributed to the conception and design of the study. Engy A. Wahsh, Amal K. Hussein, Ahmed A. Gomaa, Mohamed Baraka and Mohie eldeen Abead contributed to the generation, collection, assembly, analysis and/or interpretation of data. Amal K. Hussein, Ahmed A. Gomaa, Engy A. Wahsh and Mohamed Baraka contributed to drafting and revision of the manuscript. Amal K. Hussein, Ahmed A. Gomaa, Engy A. Wahsh , Mohamed Baraka and Mohie eldeen Abead approved the final version of the manuscript.

The authors declare that they have no conflict of interest

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