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Efficacy and Safety in Difference Combination of Sofosbuvir in Treatment of Chronic Hepatitis C Virus

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Abstract

Background: Hepatitis C virus infects about 185 million people equating 2.8% of worldwide population. Management of chronic HCV patients traditionally depended on combination of peg-interferon (IFN) with ribavirin but this regimen showed many serious side effects beside its non-satisfactory efficacy. In 2013, a second generation of direct acting antiviral agents (DAAs) gave a promising efficacy and safety. Although many IFN free regimens were approved, further evaluations are needed for these regimens.

Aim of Study: To compare safety and efficacy of Sofosbuvir in combination with Daclatasvir (DCV) or Ledipasvir (LDV) or Simeprevir (SIM) in treatment of chronic HCV patients.

Patients and Methods: This is a prospective study conducted on 150 patients of chronic HCV who visited Al-Ahrar Educational Hospital in Zagazig National Committee for the Control of Viral Hepatitis (NCCVH) from January to September of 2017 and were selected according to the inclusion and exclusion criteria set by the (NCCVH).

Patients were assigned into three groups: 50 patients received (SOF/DCV ± RBV), 50 patients received (SOF/LDV ± RBV) and 50 patients received (SOF/SIM ± RBV). Three regimens were given for 12 weeks.

Results: In this study, the mean age of the 50 patients of each group was (52.6±9 years) in SOF/DCV group, (48.2± 13.5 years) in SOF/LDV group and (50.26± 10.6 years) in SOF/SIM. A total of 150 patients including 93 (62%) males & 57 (38%) females.

Adverse events occurred in (18%) of SOF/DCV group, (18%) of SOF/LDV group and (40%) of SOF/SIM group. The most common adverse events occurred in three groups were; hyperbilirubinemia (20%) in SOF/SIM group, (8%) in SOF/DCV group and (4%) in SOF/LDV group (Table 2), thus SOF/SIM group showed a higher incidence of adverse events occurrence but adverse events in three groups were mild (not sever enough to cause treatment discontinuation).

Sustained Virological Response (SVR) rate was nearly similar in three groups: (100%) of SOF/LDV group, while it was achieved (98%) of SOF/SIM group and (98%) of SOF/DAC group. This results showed no statistically significant difference.

Conclusions: Sofosbuvir based antiviral regimen in combination with (DCV, LDV and SIM) were tolerable with no obvious side effect and showed high efficacy in management of chronic HCV with nearly similar SVR.

Key Words: *Hepatitis virus C – Direct acting antivirals – Sofosbuvir – Daclatasvir – Ledipasvir – Simeprevir.*

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Introduction

HEPATITIS C virus infection is a globally endemic disease infecting about 185 million people equating 2.8% of worldwide population [1]. Africa and specifically Egypt had the highest prevalence but the prevalence in Egypt declined to be 10% of the population who had positive HCV antibody and 7% who had positive HCV-RNA [2]. The disease commonly presents as asymptomatic chronic infection or with its complications. Morbidity and mortality are high as a result of complications including: GIT bleeding varices, hepatic encephalopathy, ascites, hepatorenal syndrome, portopulmonary hypertension and any of these complications can be the first clinical presentation of the disease [3]. Management of chronic HCV patients traditionally depended on combination of peg-interferon with ribavirin but this regimen showed many side effects, the most serious of them are hematological abnormalities [4], beside low efficacy of this combination especially in genotypes 1 and

4 of the virus (SVR rates 40-50%) [5]. In 2013, a second generation of DAAs gave a promising better efficacy and safety. Their development was depended on understanding the essential functions of encoded nonstructural viral proteins in HCV life cycle and these proteins became the targets of the new DAAs action and thus inhibit the viral replication cycle [6]. Many IFN free regimens were approved, but further studies were needed to evaluate their safety & efficacy on different HCV genotypes.

The aim: To compare safety and efficacy of Sofosbuvir in combination with Daclatasvir or Ledipasvir or Simeprevir in treatment of chronic HCV patients.

Patients and Methods

Patients: This is a prospective study conducted on 150 patients of chronic HCV who visited the Viral Hepatitis Center in Al-Ahrar Educational Hospital in Zagazig [National Committee for the Control of Viral Hepatitis (NCCVH)] from January to September of 2017 and were selected according to the inclusion and exclusion criteria set by the (NCCVH).

The inclusion criteria: Which included: Age (from 18 to 70 years), naïve or experienced HCV RNA positivity.

Exclusion criteria were: Patients with class B or C of Child-Turcotte-Pugh classification, platelet count <50000/mm^3, total serum Bilirubin >3mg, Serum Albumin <2.8g/dl, INR ≥1.7, serum creatinine ≥2.5mg/dl and pregnancy or inability to use effective contraception.

Study design:

Patients were classified into three groups:

- *Group A:* Included 50 patients received SOF 400mg once daily + DCV 60mg once daily ± Ribavirin (weight based; 1200mg if ≥75Kg or 1000mg if <75 Kg of bodyweight) for 12 weeks.
- *Group B:* Included 50 patients received SOF 400mg once daily + LDV 90mg once daily ± Ribavirin (weight based; 1200mg if ≥75Kg or 1000mg if <75Kg of bodyweight) for 12 weeks.
- *Group C:* Included 50 patients received: SOF 400mg once daily + SIM 150mg once daily ± Ribavirin (weight based; 1200mg if ≥75Kg or 1000 mg if <75Kg of bodyweight) for 12 weeks.

All patients were informed about the study protocol and informed written consents were obtained from them. The protocol was evaluated and approved by Ethical Committee of Benha Faculty of Medicine.

Monitoring of treatment efficacy:

- HCV quantitative PCR was done before starting the treatment, at week 4 from starting treatment (Rapid Virological Response (RVR), at the end of treatment (End of Treatment Response (ETR), and at week 12 after the end of treatment (Sustained Virological Response (SVR).
- Virological response was considered when HCV RNA is below the lower limit of detection at the end of treatment and after 12 weeks from end of treatment (SVR).
- Treatment failure was defined as: Viral non response: HCV RNA persistently above lower limit of detection at end of treatment.
- Viral relapse was defined as confirmed HCV RNA above lower limit of detection during the follow-up period for patients who achieved HCV RNA below lower limit of detection at the end of treatment [7].

Safety assessment:

Side effects of the drugs were analyzed by careful history taking through clinical examination and the results of standard laboratory testing which were performed and registered at each visit during treatment and during follow up periods after therapy completion including weeks 0, 4, 8 and 12 and post-treatment weeks 12.

Statistical methods:

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS Version 20.0) (Statistical Package for the Social Sciences) software for analysis. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, the following tests were used to test differences for significance. Differences between parametric quantitative paired groups by paired *t*-test in non parametric by sign. Multiple parametric by ANOVA non parametric by Kruskal Wallis, *p*-value was set at <0.05 for significant results.

Results

In this study, first group included 50 patients [27 male (54%) and 23 female (46%), their mean age was 52.6±9.06 years] had received SOF/DCV (only 4 patients added ribavirin), second group included 50 patients [30 male (60%) and 20 female (40%), their mean age was 48.2 ± 13.5 years] had received SOF/LDV without ribavirin and third group included 50 patients [36 male (72%) and 14 female (28%), their mean age was 50.2 ± 10.6 years] had received SOF/SIM without ribavirin with no statistically significant difference between three groups.

Also treatment status in this study: 146 naïve patients and 4 patients (2.7%) of total 150 patients were experienced (previously non responders to PEG-IFN plus ribavirin), and showed no statistically significant difference between three groups.

Regarding safety assessment, results of the standard follow-up laboratory tests revealed that three regimens in this study showed adverse events occurrence in 9 patients (18%) of SOF/DCV group, 9 patients (18%) of SOF/LDV group and 20 patients (40%) of SOF/SIM group. The most common adverse events occurred in three groups were;

- Hyperbilirubinemia in 4 patients (8%) in SOF/DCV group, 2 patients (4%) in SOF/LDV group and 10 patients (20%) in SOF/SIM group.
- Headache in 2 patients (4%) in group SOF/DCV, 4 patients (8%) in SOF/LDV group and 1 patients (2%) in SOF/SIM group.
- Anemia in 1 patient (2%) in SOF/DCV group, 2 patients (4%) in SOF/LDV group and 3 patients (6%) in SOF/SIM group (Table 2).

In this study no obvious side effect (not severe enough to cause treatment discontinuation).

There was significant decrease of mean serum ALT and AST levels among three groups (mean serum ALT in SOF/DCV group was 46.5IU/L before starting treatment and 32.1IU/L after 12 weeks from starting treatment and in SOF/LDV group was 40.5IU/L before starting treatment and 31.9IU/L after 12 weeks from starting treatment and in SOF/SIM group it was 54.6IU/L before starting treatment and 29.2IU/L after 12 weeks from starting treatment).

The mean serum AST in SOF/DCV group was 50.1IU/L before starting treatment and 32.2IU/L after 12 weeks from starting treatment and in SOF/LDV group was 39.9IU/L before starting treatment and 31IU/L after 12 weeks from starting treatment and in SOF/SIM group it was 50IU/L before starting treatment and 27IU/L after 12 weeks from starting treatment.

Although Hb were within the normal range in three groups before and after treatment but it was statistically significantly decrease in SOF/DCV group only before and after treatment, also serum bilirubin was highly in SIM/SOF with statistically significant before and after treatment.

All patients in SIM/SOF group, had achieved RVR (50/50) patients (100%) while it was achieved (49/50) patients (98%) of SOF/DCV group and (49/50) patients (98%) of SOF/LDV group (Table 4). The baseline factors including (the type of the regimen, patient's sex, patient's treatment status, the baseline viral load, platelet count and presence of cirrhosis) were not statistically significant in predicting RVR.

Regarding efficacy assessment, the End of Treatment Response (ETR) rate of three groups response was (100%, 100% and 98%) for (SOF/SIM±RBV, SOF/LDV±RBV and SOF/DCV±RBV) respectively. Only one patient in SOF/DCV group had a virological failure. These results showed no statistically significance ($p>.05$) (Table 4). Previously mentioned baseline factors showed no statistically significant in predicting ETR.

Sustained Virological Response (SVR) rate was 50 patients (100%) of SOF/LDV group, while it was achieved 49 patients (98%) of SOF/SIM group and 49 patients (98%) of SOF/DAC group. These results showed no statistically significant difference. ($p>.05$) (Table 4). Previously mentioned baseline factors showed no statistically significant difference in sustained virological response prediction.

Table (1): General history data of the patients.

	SOF + DCV	SOF + LDV	SOF + SIM	χ^2	*p*
Age:					
(Mean ± SD)	52.6±9.04	48.2±13.5	50.2±10.6	1.929	0.14
Sex:					
Male	27 (54%)	30 (60%)	36 (72%)	3.56	0.16
Female	23 (46%)	20 (40%)	14 (28%)		
BMI:					
(Mean ± SD)	26.3±4.1	27.1±3.5	27.6±3.7	0.175	0.83
Traetment status:					
Experience	2 (4%)	1 (2%)	1 (2%)	0.51	0.77
Naive	48 (96%)	49 (98%)	49 (98%)		

BMI : Body Mass Index, calculated as weight in kilograms divided by the height in meters squared.
SOF/DCV : Sofosbuvir, Daclatasvir group.
SOF/LDV : Sofosbuvir, Ledipasvir group.
SOF/SIM : Simeprevir, Sofosbuvir group.

Table (2): Documented side effects of each group.

Side effects	SOF + DCV N (%)	SOF + LDV N (%)	SOF + SIM N (%)	Total	*p*-value
Headache	2 (4%)	4 (8%)	1 (2%)	7 (4.66%)	0.218
Skin Rash	1 (2%)		2 (4%)	3 (2%)	0.337
Pruritus			2 (4%)	2 (1.33%)	0.236
Hyperbilirubinemia	4 (8%)	2 (4%)	10 (20%)	16 (10.66%)	0.011*
Bleeding tendency			2 (4%)	2 (1.33%)	0.236
Anemia	1 (2%)	2 (4%)	3 (6%)	6 (4%)	0.193
Thrombocytopenia	1 (2%)	1 (2%)	–	2 (1.33%)	0.541
Total	9 (18%)	9 (18%)	20 (40%)	38 (25.33%)	0.153

Table (3): Comparison between the mean serum levels of AST, ALT, bilirubin, hemoglobin level, WBCs count and platelet count before and after treatment in three groups

Variables	Before treatment	After treatment	*p*-value
Mean serum ALT (IU/L):			
SOF/DAC (mean ± SD)	46.5±18.8	32.1±7.9	0.000*
SOF/LDV (mean ± SD)	40.5±17.5	31.9±9	0.000*
SOF/SIM (mean ± SD)	50±26	29±15	0.000*
Mean serum AST (IU/L):			
SOF/DAC (mean ± SD)	50.1±24	32.2±7.9	0.000*
SOF/LDV (mean ± SD)	39.9±17	31±9.8	0.001*
SOF/SIM (mean ± SD)	50±24	27±11	0.000*
Mean serum Bilirubin (mg/dl):			
SOF/DAC (mean ± SD)	0.77±0.39	0.87±0.23	0.26
SOF/LDV(mean ± SD)	0.48±0.19	0.88±0.15	0.33
SOF/SIM (mean ± SD)	0.87±0.43	2.9±1.31	0.027*
Mean hemoglobin level (g/dl):			
SOF/DAC (mean ± SD)	13.64±1.54	12.85±1.04	0.001*
SOF/LDV (mean ± SD)	13.4±1.49	13.2±1.6	0.133
SOF/SIM (mean ± SD)	14.1±1.3	12±1.2	0.277
Mean WBCs count (L/mcl):			
SOF/DAC (mean ± SD)	6872±1711	6534±2013	0.288
SOF/LDV (mean ± SD)	6789±2506	6251±1897	0.162
SOF/SIM (mean ± SD)	5785±1615	5761±1342	0.190
Mean platelet count (L/mcl):			
SOF/DAC (mean ± SD)	197000±70132	188760±48264	0.209
SOF/LDV (mean ± SD)	166690±67997	179860±59811	0.088
SOF/SIM (mean ± SD)	195540±48530	188360±35911	0.117

*: The significant *p*-value is <0.05.

Table (4): Efficacy endpoints assessment results.

Groups	Rapid Virologic Response (RVR)	End Treatment Response (ETR)	Sustain Virologic Response (SVR)
SOF/DCV	49 (98%)	49 (98%)	49 (98%)
SOF/LDV	49 (98%)	50 (100%)	50 (100%)
SOF/SIM	50 (100%)	50 (100%)	49 (98%)
Total	148 (98.66%)	149 (99.33%)	148 (98.66%)
p-value	0.496	1	0.49

The significant *p*-value is <0.05.
SOF/DCV : Sofosbuvir, Daclatasvir group.
SOF/LDV : Sofosbuvir, Ledipasvir group.
SOF/SIM : Sofosbuvir, Simeprevir group.

Discussion

Management of chronic HCV patients traditionally depended on combination of peg-interferon with ribavirin but this regimen showed many serious side effects beside its non-satisfactory efficacy. In 2013, a second generation of DAAs gave a promising efficacy and safety. Although many IFN free regimens were approved by FDA, AASLD and EASL, further evaluations are needed for these regimens.

Concerning the safety assessment in this study; in SIM/SOF group, the most common adverse events occurred in this group were: Anemia (6%), rash (4%) and headache, 10 cases got hyperbilirubinemia at week 4 and 8 during treatment course. In similar studies such as Pearlman and his colleagues **[8]** and El-Khayat and his colleagues were done for assessing the same combination therapy revealed similar adverse events but with different percentages which mostly are due to the different number of the patients in each study **[9]**.

In SOF/LDV group, the most common adverse events occurred were: Headache (8%), anemia (4%), rash (4%) and hyperbilirubinemia, in similar studies Mizokami and his colleagues **[10]** and Afdhal and his colleagues revealed same adverse events of this study but with different percentages which mostly are due to there are many points of differences in the comparison between this study and the previously mentioned studies such as the randomization of HCV genotyping of participants in each comparable study and the different number of patients in each study **[11]**.

In SOF/DCV group, the most common adverse events occurred in this group were: Hyperbilirubinemia (8%), headach (4%), rash and anemia, adverse evants were not sever enough to cause treatment discontinuation, in similar studies such Hill and his colleagues and Sulkowski and his colleagues, revealed same adverse events of this study **[12,13]**.

In this study, the combination of [SOF/DCV, SOF/LDV, SOF/SIM] showed a highly rate of sustained virologic response (SVR 12; 98%, 100%, 98%) respectively, but with no statistical significance ($p>0.05$).

Efficacy in this study was identical to Hill and his colleagues with 616 patients HCV in sofosbuvir-based regimens were assessed there was 146 patients treated by SOF/DCV ±RBV for 12 weeks SVR (98%) and 104 patients treated by SOF/LDV ± RBV for 12 weeks SVR (100%) which included

naïve or experienced, cirrhotic and non-cirrhotic patients [12].

Results in this study are higher than those reported by Shin and other colleagues with Sofosbuvir-Based Regimens on patients infected by HCV genotype 1, the SVR rate was 92.2% for SOF/LDV, 87.0% of SIM/SOF group cirrhotic and non cirrhotic naïve or previous experienced patients to ribavirin plus PEG-IFN [14].

The differences may be referred to the difference in the HCV genotypes of both studies, as the most common HCV genotype prevalent in Egypt is genotype 4 of HCV. Additionally, some studies revealed that DAAs treatment failure is higher in HCV GT1 infected patients than those of HCV GT4 [15].

Efficacy result of SIM/SOF therapy in our study (SVR is 98%) was lower than El-Raziky and his colleagues which conducted on 63 patients in Egypt (SVR100%) [16] and also Buti and his colleagues conducted on 40 patients in Spain (SVR100%) [17]. SVR result of this study was higher than El-Khayat and his colleagues conducted on 583 patients infected by HCV G-4 in Egypt (SVR 95%) [9]. It was also higher than Eletreby and his colleagues which the first 6211 cohort of Egyptian patients which revealed SVR of 94% [18] and also higher than SVR of Willemse and his colleagues which conducted on 53 patients infected by HCV GT4 in Amsterdam which was 92% [19].

All studies SOF/SIM therapy which compared to ours included naïve, experienced, cirrhotic and non-cirrhotic patients. That points of difference between this study and pervious studies may be due to randomization of the participants numbers and beside the randomization of HCV genotyping may be referred to difference in HCV genotyping of all studies, the most common HCV genotype prevalent in Egypt is HCV GT4 which was confirmed by many epidemiological studies [20-22] but still further more wide studies needed.

The efficacy of SOF/DCV in this present study SVR (98%) was identical to Sulkowski and his colleagues which conducted on 44 patients infected with HCV SVR (98%), GT1 experience patients [13]. In contrary SVR result of this study was higher than Hézode and his colleagues SVR (91%) conducted on 215 patients infected with HCV, GT4 [23], and Bourliere and his colleagues SVR (92%) that was conducted on 194 patients infected with HCV GT1 [24].

The efficacy of SOF/LDV in this present study SVR (100%) was identical to. Kohli and his colleagues was conducted on 10 patients HCV,GT4 compensated cirrhotic patients [25], and to Mizakami and his colleagues was conducted on 171 patients in Japan [10].

In contrary SVR results of this present study SOF/LDV is higher than Abergel and his colleagues SVR (93%) conducted on 44 patients HCV, GT4, 22 patient experience, (23%) compensated cirrhotic. [26] and Kohli and his colleagues SVR (95%) which conducted on 21 HCV, GT4, naïve or experience, non cirrhotic or compensated cirrhotic [25], and also Afdhal and his colleagues in ION 1 study SVR (99%) which conducted on 214 patients HCV, GT1 naïve patients [27,28], also Afdhal and his colleagues ION 3 study SVR (95%) which conducted on 216 patients HCV, GT1 [11].

Conclusion:

Sofosbuvir based antiviral regimen in combination with (DCV, LDV and SIM) were tolerable with no obvious side effect and showed high efficacy in management of chronic HCV with nearly similar SVR.

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دراسة الفعالية والآمان والردة فى مريض الفيروس الكبدى سى عن طريق العلاج بالسوفوسبوفير مع كلا من الدكلاتاسيفير والليديباسفير والسيميبرفير

فيروس إلتهاب الكبد ج يصيب نحو ١٨٥ مليون شخص فى جميع أنحاء العالم حسب آخر تقديرات خلال السنوات ال ١٥ الآخيرة. ويعد العرض الإكلينيكى الآكثر شيوعا للمرض هو العرض المزمن ومضاعفاته مثل: تليف الكبد، وإرتفاع ضغط الدم بالوريد البابى الكبدى وسرطان الكبد. وقد كانت الخطة العلاجية لمرض الإلتهاب الكبدى المزمن بفيروس (سى) تعتمد على مزيج من عقار الريبافيرين مع الإنترفيرون ولكن هذا النظام العلاجى أظهر العديد من الآثار الجانبية الخطيرة بجانب إنخفاض فعالية هذا النظام العلاجى. ولكن فى عام ٢٠١٣، نشأ جيل ثانى من المضادات الفيروسية المباشرة أعطت نتائج واعدة من حيث الفعالية والآمان.

تهدف هذه الدراسة إلى مقارنة نظام العلاج بعقار السوفوسبوفير مع كلا من الدكلاتاسيفير والليديباسفير والسيميبرفير فى علاج المرضى بالإلتهاب الكبدى الفيروسى سى من حيث الفعالية والآمان والردة. هذه الدراسة تم إجرائها على ١٥٠ مريض من المرضى الذين تم قبولهم فى وحدة علاج الفيروسات الكبدية بمستشفى الآحرار التعليمى بالزقازيق. وقد تم إختيار المرضى وفقا لمعايير الإدراج والإستبعاد المجددة من قبل الوحدة. وقد أظهرت هذه الدراسة سلامة وفعالية النظام العلاجى المتضمن عقار (السوفوسبوفير مع أحد المضادات الفيروسية المباشرة الآخرى مثل الدكلاتاسيفير والليديباسفير والسيميبرفير) لمدة ١٢ أسبوع أظهر سلامة وفعالية فى الشفاء، كما أظهرت هذه الدراسة أهمية (الإستجابة الفيروسية السريعة للعلاج) فى التنبؤ بالشفاء التام بعد الإنتهاء من الفترة الزمنية المحددة للنظام فى النظم العلاجية التى تعتمد على السوفوسبوفير ولكن هناك حاجة لمزيد من الدراسات لتأكيد قيمته التنبؤية.