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Efficacy, Safety and Relapse of Sofosbuvir in Combination with Daclatasvir, Ledipasvir and Simeprevir for Treatment of Hepatitis C Virus in Egypt

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Abstract

Background: Hepatitis C Virus infects about 185 million people equating 2.8% of worldwide population and about 500,000 people die annually from hepatitis C related liver diseases. The most common clinical presentation of the disease is the chronic hepatitis and its complications such as: Compensated cirrhosis, portal hypertension, decompensated cirrhosis and Hepatocellular Carcinoma (HCC). Therapeutic 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: To compare sofosbuvir in combination with Daclatasvir, Ledipasvir and Simeprevir in patients with chronic hepatitis C infection according to safety, efficacy, relapse and patient outcomes.

Patients and Methods: This is a prospective study conducted on 150 patients of chronic HCV who were admitted to the Viral Hepatitis Center in Al-Ahrar Educational Hospital in Zagazig {National Committee for the Control of Viral Hepatitis (NCCVH) during the first 9 months of 2017 and were selected according to the inclusion and exclusion criteria set by the (NCCVH). 58% of overall participants had cirrhosis and 2.7% were treatment-experienced. Patients were assigned into three groups: 50 patients received Sofosbuvir + Daclatasvir ± Ribavirin (SOF/DCV ± RBV) therapy, 50 patients received Sofosbuvir + Ledipasvir ± Ribavirin (SOF/LDV ± RBV) therapy and 50 patients received Sofosbuvir + Simeprevir ± Ribavirin (SOF/SIM±RBV) therapy. Three regimens were given for 12 weeks. Primary end point was the rate of achieving SVR12 by HCV RNA PCR, while secondary end point was the occurrence of virologic relapse.

Results: The SVR rate of three groups was 98%, 100% and 100% for SOF/DCV, SOF/LDV and SOF/SIM groups respectively. Only one patient had a virological failure and he was in SOF/DCV group but these results showed no statistical significance. Virological relapse occurred in only 1 patients (.67%) of the 149 patients. The patient who showed virological failure wasn't included, while the only one patient relapsed (2%) was in SOF/SIM therapy group. Results of virological relapse were statistically not significant. RVR showed a predictive value in SVR achievement and relapse occurrence was also confirmed in our study, in SVR (p=>.05) and in relapse (p=.9). Adverse events occurred in (22%) of SOF/DCV group, (26%) of SOF/LDV group and (40%) of SOF/SIM group (p=.153), thus SOF/SIM therapy showed a higher incidence of adverse events occurrence.

Conclusions: Sofosbuvir based antiviral combination therapy with (DCV, LDV and SIM) showed a highly safety, tolerability and efficacy for treatment of chronic Hepatitis C Virus.

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

Introduction

HEPATITIS C Virus infection is a globally endemic disease infecting about 185 million people equating 2.8% of worldwide population [1]. About 500,000 people die annually from hepatitis-c related liver diseases [2]. Africa and specifically Egypt

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Abbreviations:

HCV	: Hepatitis C Virus.
DAAs	: Direct Acting Antiviral agents.
RVR	: Rapid Virologic Response.
SVR	: Sustained Virologic Response.
SVR12	: Sustained Virologic Response 12 weeks after therapy completion.
FDA	: The Food and Drug Administration.
AASLD	: American Association for the Study of Liver Diseases.
EASL	: European Association for the Study of the Liver.

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 [3]. The disease commonly presents as asymptomatic chronic infection or with its complications. Morbidity and mortality are high as a result of complications including: Bleeding varices, hepatic encephalopathy, ascites, hepatorenal syndrome, portopulmonary hypertension and any of these complications can be the first clinical presentation of the disease [4]. Therapeutic management of chronic HCV patients traditionally depended on combination of peginterferon with ribavirin but this regimen showed many side effect the most serious of them are hematological abnormalities [5], beside low efficacy of this combination especially in genotypes 1 and 4 of the virus (SVR rates 40-50%) [6]. 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 [7]. Many IFN free regimens were approved, but further studies were needed to evaluate their safety and efficacy on different HCV genotypes.

The aim: To compare sofosbuvir in combination with Daclatasvir, Ledipasvir and Simpervir in patients with chronic hepatitis C infection according to safety, efficacy, relapse and patient outcomes.

Patients and Methods

This is a prospective study was conducted on 150 patients of chronic HCV who were admitted to the Viral Hepatitis center in this is a prospective study conducted on 150 patients of chronic HCV who were admitted to the Viral Hepatitis Center in Alahrar Educational Hospital in Zagazig {National Committee for the Control of Viral Hepatitis (NCCVH)} during the first 9 months of 2017 and were selected according to the inclusion and exclusion criteria set by the (NCCVH). Inclusion criteria included: Age: 18-70 years, HCV RNA positivity, any BMI, treatment naïve or treatment experienced.

Exclusion criteria: 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 Sofosuvir 400mg once daily + Daclatsvir 60mg once daily ± Ribavirin (weight based; 1200mg if ≥75Kg or 1000mg if <75Kg of bodyweight) for 12 weeks. Group B: Included 50 patients received Sofosuvir 400mg once daily + Ledibasvir 90mg once daily ± Ribavirin (weight based; 1200mg if ≥75Kg or 1000mg if <75Kg of bodyweight) for 12 weeks. Group C: Included 50 patients received: Sofosbuvir 400mg once daily + Simeprevir 150mg once daily ± Ribavirin (weight based; 1200mg if ≥75Kg or 1000mg 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.

Efficacy assessment:

Was done through sustained virologic response (SVR 12) (defined as undetectable HCV RNA levels 12 weeks after therapy completion) and occurrence of virologic relapse (defined as HCV-RNA concentration greater than 16IU at any time of post treatment follow-up period after documentation of HCV-RNA level of less 16IU in serum sample at end of treatment) [8].

Safety assessment:

Side effects of the drugs and the results of standard laboratory testing were performed and registered at each visit during treatment and during follow-up periods after therapy completion including weeks 0, 2, 4, 8 and 12 and post-treatment weeks 4, 12 [9].

Clinical end points:

Primary end point was the rate of achieving SVR. Secondary clinical end point of efficacy was the rate of treatment failure at specified time points during and after treatment. Safety end points include: The frequency of adverse events and its severity, the safety of treatment according to the standard follow-up laboratory tests and treatment discontinuation due to severe adverse events.

Statistical methods:

Data were analyzed using the Statistical Package for Social Sciences (SPSS Ver.20 Chicago, IL, USA). The distributions of quantitative variables were tested for normality using Kolmogorov-Smirnov test. Normally distributed data was described using mean and standard deviation, while data was described using median and range. Qual-

itative data were described using number and percent. Comparing quantitative normally distributed variables repeated >2 times was conducted using repeated ANOVA test followed by post hoc test. If results were significant. Comparing quantitative not normally distributed variables repeated >2 times was conducted using Friedman ANOVA test. Independent sample *t*-test was used to compare quantitative data between the 3 groups. Pearson Chi square used to compare 2 X 2 categorical variables. Fisher's Exact test is used if >20% of cells had expected cell count less than 5. In >2 X 2 table we used Monte Carlo significance test if >20% of cells had expected cell count less than 5. Logistic regression model was used for prediction of virological response. Important significant predictors by univariate analysis were entered in the model. Mcnemar test was used when there was a significant difference between proportions in 2 paired variables. In all statistical tests, level of significance of 0.05 is used, below which the results considered to be statistically significant.

Results

Regarding efficacy assessment, SVR rate of three groups were (98%, 100% and100%) for (SOF/DCV±RBV, SOF/LDV±RBV, SOF/SIM±RBV) respectively. Only one patient had a virological failure and he was in SOF/DCV group. These results statistically showed no significance (p >.05) as shown in (Table 2). 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 SVR. All patients in SIM/SOF group, had achieved RVR (50/50) while it was achieved (49/50) patients of SOF/DCV group and (49/50) patients of group (p=0.496) as shown in (Table 2). Previously mentioned baseline factors showed no statistically significant difference in RVR. Virological relapse assessment revealed that relapse occurred in only 1 patient (0.67%) of the 149 patients developed primary response. The only one patient relapsed with a percentage (2%) of SIM/SOF group (p>.05) as shown in (Table 2), none of 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) was statistically of significance in predicting the virological relapse.

The overall achievement RVR was found as a strong predictor for both SVR achievement and relapse occurrence.

Regarding safety assessment, results of the standard follow-up laboratory tests revealed that three regimens resulted in improvement in liver enzymes as the mean in serum ALT was 46.5 ± 18.8, 40.5± 17.5 and 54.6±26.9 and declined after 12 weeks of therapy to 32.1 ±7.9, 31.9± 17 and 29.2± 15.1 in SOF/DCV group, SOF/LDV group and SOF/SMV group respectively (p<.001). In group SOF/DCV: There was a statistical significant elevation of serum bilirubin but within its normal range as the mean was 0.77±0.39 and increased at the 12th week of therapy to 0.87±0.23 (p<0.026), there was decrease in the level of serum albumin level as the mean was 4.44± .36 and declined to 4.21± .32 after 12 weeks of therapy with statistical significance (p<0.001), there was decrease of Hb with statistical significance (p<0.001) and there was no statistical significant effect of the SOF/DCV regimen on serum creatinine level, INR and other hematological parameters (level of white blood count and platelets count), while in SOF/LDV group: There was decrease in the level of serum albumin as the mean was 4. 19 ±0.47 and declined to 4.08±0.46 after 12 weeks of therapy with statistical significance (p<0.004). There was a significant decrease in PT with statistical significance (p <0.001), and There was no statistical significant effect of the SOF/LDV regimen on serum creatinine level or the levels of Hb, WBCs, Platelate, total bilirubin and INR level, while in SOF/SIM group: Were statistically significant increased Platelete count (p<0.001). There was no statistical significant effect on serum creatinine level or the levels of Hb, WBC, PT, INR, total bilirubin and serum albumin. The study showed adverse events occurrence in 11 patients (22%) of SOF/DCV group, 13 patients (26%) of SOF/LDV group and 20 patients (40%) of SOF/SIM group (p=.153). The most common adverse events occurred in SOF/DCV group were: Hyperbilirubinemia in 4 patients (8%), headach in 2 patients (4%), fatigue in 2 patients (4%), rash in 1 patient (2%), anemia in 1 patient (2%) and thrombocytopenia in 1 patient (2%). Regarding SOF/LDV group, the most common adverse events occurred were: Headach in 4 patients (8%), fatigue in 4 patients (8%), anemia in 2 patients (4%), rash in 2 patients (4%), hyperbilirubinemia in 2 patient (4%) and thrombocytopenia in 1 patient (2%). SOF/SIM group, the most common adverse events occurred in this group were: Hyperbilirubinemia in 10 patients (20%), anemia in 3 patients (6%), rash in 2 patient (4%), renal impairment in 2 patients (4%), bleeding tendency in 2 patients (2%), and headach in 1 patient (2%). In this study the developed side effects were not severe enough to cause treatment discontinuation.

Table (1): Demographic general history data of the participants.

	SOF + DCV	SOF + LDV	SOF + SIM	χ^2	*p*
Age:					
(M ± 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
Femal	23 (46%)	20 (40%)	14 (28%)		
BMI:					
(M ± 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): Efficacy endpoints assessment results.

	SOF + DCV	SOF + LDV	SOF + SIM	Test value	*p*
• *RVR (rapid virologic response) after 4Ws:*					
- *HCV PCR:*					
[Positive >15UL/ml] N (%)	1 (2%)	1 (2%)	0 (0%)		
[Negative <15UL/ml] N (%)	49 (98%)	49 (98%)	50 (100%)	.705	.496
- Total patients	50 (100%)	50 (100%)	50 (100%)		
• *SVR (sustained virologic response) after 12Ws:*					
- *HCV PCR:*					
[Positive >15UL/ml] N (%)	1 (2%)	0 (0%)	0 (0%)		
[Negative <15UL/ml] N (%)	49 (98%)	50 (100%)	50 (100%)	–	FEP=1
- Total patients	50 (100%)	50 (100%)	50 (100%)		
• *Virological relapse: Up to 24Ws:*					
- *HCV PCR:*					
[Positive >15UL/ml] N (%)	0 (0%)	0 (0%)	1 (2%)		
[Negative <15UL/ml] N (%)	49 (100%)	50 (100%)	49 (98%)		FEP=.9
- Total patients	49 (100%)	50 (100%)	50 (100%)		

The significant *p*-value is <0.05.
SOF/DCV: Sofosbuvir, Daclatasvir group.
SOF/LDV: Sofosbuvir, Ledipasvir group.
SOF/SIM: Sofosbuvir, Simeprevir group.
FEP : Fisher's Exact test *p*-value.

Table (3): Documented adverse events of each group.

Advers events	SOF + DCV N (%)	SOF + LDV N (%)	SOF + SIM N (%)	Total
Anemia	1 (2%)	2 (4%)	3 (6%)	6 (4%)
Thrombocytopenia	1 (2%)	1 (2%)		2 (1.33%)
Fatigue	2 (4%)	4 (8%)		6 (4%)
Skin rash	1 (2%)		2 (4%)	3 (2%)
Bleeding tendancy		–	2 (4%)	2 (1.33%)
Renal impairment			2 (4%)	2 (1.33%)
Headache	2 (4%)	4 (8%)	1 (2%)	7 (4.66%)
Hyperbiliburinemia	4 (8%)	2 (4%)	10 (20%)	16 (10.66%)
Total	11 (22%)	13 (26%)	20 (40%)	44 (29.33%)

Discussion

Therapeutic 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. In this study, the combination of Sofosbuvir with Daclatasvir, Ledipasvir and Simeprevir [SOF/DCV, SOF/LDV, SOF/SIM] showed a highly rate of sustained virologic response (SVR; 98%, 100%, 100%) respectively, but with no statistical significance (p>0.05). Many patients of this study had characteristics was traditionally known to be associated with a lower rates of response, as about 38.7% of overall patients had cirrhosis, 2.4% were previous non responders to PEG-IFN plus ribavirin (experienced) and the mean of the baseline HCV-RNA level for all participants was 1.188 X 10^6 IU/ml (>400.000IU/ml) [10]. Efficacy in this study was identical to three buyer's study 616 patients HCV G1, 2, 3, 4, 5, 6 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 [11].

Results in this study are higher than those reported by Real-World Single-Center Experience with Sofosbuvir-Based Regimens on patients infected by HCV genotype 1 in Virginia Mason Medical Center which the SVR had cirrhosis. 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 [12]. These 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 [16]. The efficacy of SOF/DCV in this present study SVR (98%) was identical to Three buyer's club study that was conducted on 146 patients infected with HCV G1, 2, 3, 4, 5, 6 naïve, (11%) compensated cirrhotic treated by SOF/DCV±RBV [11] and AI444040 study that was conducted on 41 patients infected with HCV, GT1 naïve patients [22] and also to ALLY-2 study conducted on 44 patients infected with HCV, GT1 experience patients [28]. In contrary SVR result of this study was higher than French ATU study SVR (91%) conducted on 215 patients infected with HCV, GT4 [27] and ANRS/AFEF HEPATHER study SVR (92%) that was conducted on 194 patients infected with HCV GT1 [30]. The efficacy of SOF/LDV in this present study SVR (100%) was identical to NIAID SYNERG study in phase 2 trial was conducted on 10 patients HCV, GT4 compensated cirrhotic patients [29] and also to three buyer's club study that was conducted on 104 patients infected with HCV G1, 2, 3, 4, 5, 6 naïve, non cirrhotic or compensated cirrhotic treated by SOF/LDV ±RBV [11] and also to Mizakami et al., (2015) study phase 3 that was conducted on 171 patients in Japan infected with HCV treated with SOF/LED without ribavirin [26]. In contrary SVR results of this present study is higher than Abergel et al., (2016) study SVR (93%) conducted on 44 patients HCV, GT4, 22 patient experience, (23%) compensated cirrhotic patients treated with SOF/LED without ribavirin [25] and NIAID SYNERGY study SVR (95%) which conducted on 21 HCV, GT4, naïve or experience, non cirrhotic or compensated cirrhotic patients treated without ribavirin [29], and also ION 1 study SVR (99%) which conducted on 214 patients HCV, GT1 naïve patients treated with SOF/LED with ribavirin [23], also ION 3 study SVR (95%) which conducted on 216 patients HCV, GT 1 compensated cirrhotic patients treated with SOF/LDV without ribavirin [24] and Real-World Single-Center Experience study SVR (92.2%) which conducted on 155 patients HCV GT1 without RBV [12]. Efficacy result of SIM/SOF therapy in our study (SVR is 100%) was identical to OSIRIS study that was conducted on 63 patients in Egypt [17] and also to PLUTO study conducted on 40 patients in Spain [18]. SVR result of our study was higher than that of large multicenter observational real-world experience study conducted on 583 patients infected by HCV G-4 in Egypt (SVR 95%) [19]. It was also higher than the first 6211 cohort of Egyptian patients which revealed SVR of 94% [20] and higher than SVR of another study conducted on 53 patients infected by HCV GT4 in Amsterdam which was 92% [21]. 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 [13-15] but still further more wide studies needed.

Concerning the safety assessment in our study in SOF/DCV group, the most common adverse events occurred in this group were: Hyperbilirubinemia (8%), headach (4%), fatigue (4%), rash

and anemia, adverse evants were not sever enough to cause treatment discontinuation, in similar studies such Hill et al., (2017) study and ALLY-2 study (2015), revealed same adverse events of this study but with different percentages which mostly are due to the different number of the participants in each study **[11,28]**. In SOF/LDV group, the most common adverse events occurred were: Headach (8%), fatigue (8%), anemia (4%), rash (4%) and hyperbilirubinemia, in similar studies Mizokami et al., (2015) & ION 3 study, revealed same adverse events of this study but with different percentages which mostly are due to the different number of the participants in each study **[24,26]**, Real-World Single-Center Experience study no skin rash and anemia, the most prominent side effects were headache and fatigue **[12]**. In SIM/SOF group, the most common adverse events occurred in this group were: Anemia (6%), rash (4%), myalgia and headach, 10 case got hyperbilirubinemia at week 4 and 8 during therapy course. In similar studies such as Pearlman et al., 2015 and El-Khayat et al., 2016 were done for assessing the same combination therapy revealed similar adverse events **[9,19]**.

Finally, inspite of the overall satisfactory response of the three regimens studied in our work, the small number of study population necessitates extension of this work through further larger sized collaborative studies including larger number of patients of different stages of liver disease and comparing other regimens of therapy.

Conclusion:

The 12 weeks regimen of Sofosbuvir base combination therapy (DCV, LDV and SIM) showed a highly safety, tolerability and efficacy. The RVR showed a predictive value in SVR12 achievement and relapse occurrence in Sofosbuvir based antiviral regimens.

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References

1- MOHD HANAFIAH K., GREOGER J., FLAXMAN A.D. and WIERSMA S.T.: Global epidemiology of hepatitis C virus infection: New estimates of age-specific antibody to HCV seroprevalence. Hepatology, 57 (4): 1333-42, 2013.

2- World Health Organization. Hepatitis C. Fact sheet no. 164. Updated July 2015. Accessed on 10 Feb 2016. http://www.who.int/mediacentre/ factsheets/fs164/en.

3- KANDEEL A., GENEDY M., EL-REFAI S., FUNK A.L. , FONTANET A. and TALAAT M.: The prevalence of hepatitis C virus infection in Egypt 2015: Implications for future policy on prevention and treatment. Liver Int., 37 (1): 45-53, 2017.

4- SHAH N.L., BANAEI Y.P., HOJNOWSKI K.L. and CORNELLA S.L.: Management options in decompensated cirrhosis. Hepat. Med., 7: 43-50, 2015.

5- LASHIN A.H., SHAHEEN Y.A., METWALLY M.A., EL-FEKY H.M., HEGAB M.F. and ABBAS S.M.: Incidence and predictors of hematological side effects in chronic HCV Egyptian patients treated with PEGylated interferon and ribavirin. Indian J. Gastroenterol., 32 (5): 316-23, 2013.

6- TENCATE V., SAINZ B. Jr., COTLER S.J., UPRICHARD S.L.: Potential treatment options and future research to increase hepatitis C virus treatment response rate. Hepat. Med., 2: 125-45, 2010.

7- PIÑEIRO D. and MARTINEZ-SALAS E.: RNA structural elements of hepatitis C virus controlling viral RNA translation and the implications for viral pathogenesis. Viruses, 4 (10): 2233-50, 2012.

8- SMITH-PALMER J., CERRI K. and VALENTINE W.: Achieving sustained virologic response in hepatitis C: A systematic review of clinical, economic and quality of life benefits. B.M.C. Infect. Dis., 15-19, 2015.

9- PEARLMAN B.L., EHLEBEN C. and PERRYS M.: The combination of simeprevir and sofosbuvir is more effective than that of peginterferon, ribavirin and sofosbuvir for patients with hepatitis C-related Child class A cirrhosis. Gastroenterology. 2015 Apr., 148 (4): 762-70, 2015.

10- WEDEMEYER H.: Hepatitis C in Mark Feldman, Lawrence S. Friedman and Lawrence J. Brandet editors of Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 10th Edition, Volume 1, published by EL SEVIR SAUNDERS, Philadelphia, U.S.A, Ch. 80: p. 1345, 2016.

11- HILL ANDREW, GITEN KHWAIRAKPAM, JAMES WANG, SERGEY GOLOVIN, VICKY HOUGHTON-PRICE, ROXANNA KOROLOGOU-LINDEN, SANJAY NATH, ANNA SAVAGE and GREG JEFFERYS: High sustained virological response rates using imported generic direct acting antiviral treatment for hepatitis C Journal of Virus Eradication, 3: 200-3, 2017.

12- SHIN HYUN PHIL, BLAIRE BURMAN, RICHARD A. KOZAREK, AMY ZEIGLER, CHIA WANG, HOUGHTON LEE, TROY ZEHR and ALICIA M.: Real-World Single-Center Experience with Sofosbuvir-Based Regimens for the Treatment of Chronic Hepatitis C Genotype 1 Patients Gut and Liver, Vol. 11, No. 5, September, pp. 711-20, 2017.

13- ABD ELRAZEK A.E., BILASY S.E., ELBANNA A.E. and ELSHERIF A.E.: Prior to the oral therapy, what do we know about HCV-4 in Egypt: A randomized survey of prevalence and risks using data mining computed analysis, 93 (28): e 204, 2014.

14- GOWER E., ESTES C., BLACH S., RAZAVI-SHEARER K. and RAZAVI H.: Global epidemiology and genotype distribution of the hepatitis C virus infection. J. Hepatol., 61 (1 Suppl): S45-57, 2014.

15- HAMED M.E., KAMAL ALANANI N.M., SHERIEF L.M., FOUAD M.A., ELWAHAB L.A. and RAAFAT N.: Study of non-organ-specific antibodies in children

with genotype 4 chronic hepatitis C. Saudi J. Gastroenterol., 19 (6): 262-70, 2013.

16- LLANERAS J., RIVEIRO-BARCIELA M., BUTI M. and ESTEBAN R.: Hepatitis C virus genotype 4: Genotype 1's little brother. J. Viral. Hepat., 24 (1): 4-12, 2017.

17- EL RAZIKY M., GAMIL M., ASHOUR M.K., SAMEEA E.A., DOSS W., HAMADA Y., VAN DOOREN G., DEMASI R., KEIM S., LONJON-DOMANEC I., HAMMAD R., HASHIM M.S., HASSANY M. and WAKED I.: Simeprevir plus sofosbuvir for eight or 12 weeks in treatment-naïve and treatment-experienced hepatitis C virus genotype 4 patients with or without cirrhosis. J. Viral. Hepat., 1-9, 2016.

18- BUTI M., CALLEJA J.L., LENS S., DIAGO M., ORTEGA E., CRESPO J., PLANAS R., ROMERO-GÓMEZ M., RODRÍGUEZ F.G., PASCASIO J.M., FEVERY B., KURLAND D., CORBETT C., KALMEIJER R. and JESSNER W.: Simeprevir in combination with sofosbuvir in treatment-naïve and-experienced patients with hepatitis C virus genotype 4 infection: A Phase III, open-label, single-arm study (PLUTO). Aliment. Pharmacol. Ther., 45 (3): 468-75, 2017.

19- EL-KHAYAT H.R., FOUAD Y.M., MAHER M., EL-AMIN H. and MUHAMMED H.: Efficacy and safety of sofosbuvir plus simeprevir therapy in Egyptian patients with chronic hepatitis C: A real-world experience. Gut., 0: 1-5, 2016.

20- ELETREBY R., ELAKEL W., SAID M., EL-KASSAS M., SEIF S., ELBAZ T., EL-RAZIKY M., ABDEL REHIM S., ZAKY S., FOUAD R., GAMAL ELDEEN H., ABDO M., KORANY M., YOSRY A., EL-SERAFY M., EL-SAYED M.H., EL-SHAZLY Y., WAKED I., DOSS W. and ESMAT G.: Real life Egyptian experience of efficacy and safety of Simeprevir/Sofosbuvir therapy in 6211 chronic HCV genotype IV infected patients. Liver Int., 1-8, 2016.

21- WILLEMSE S.B., BAAK L.C., KUIKEN S.D., VAN DER SLUYS VEER A., LETTINGA K.D., VAN DER MEER J.T., DEPLA A.C., TUYNMAN H., VAN NIEUWKERK C.M., SCHINKEL C.J., KWA D., REESINK H.W. and VAN DER VALK M.: Sofosbuvir plus simeprevir for the treatment of HCV genotype 4 patients with advanced fibrosis or compensated cirrhosis is highly efficacious in real life. J. Viral. Hepat., 23 (12): 950-4, 2016.

22- SULKOWSKI M.S., GARDINER D.F. and RODRIGUEZ-TORRES M.: Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N. Engl. J. Med., 370: 211, 2014.

23- AFDHAL N., REDDY K.R. and NELSON D.R.: Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N. Engl. J. Med., 370 (16): 1483-93, 2014.

24- AFDHAL N., ZEUZEM S., KWO P., CHOJKIER M., GITLIN N. and PUOTI M.: Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N. Engl. J. Med., 370: 1889-98, 2014.

25- ARMAND ABERGEL, SOPHIE METIVIER DIDIER SAMUEL DEYUAN JIANG, KATHRYN KERSEY, PHILLIP S. PANG, EVGUENIA SVAROVSKAIA, STEVEN J. KNOX, VERONIQUE LOUSTAUD-RATTI and TARIK ASSELAH: Ledipasvir Plus Sofosbuvir for12 Weeks in Patients With Hepatitis C. Genotype 4 Infection Hepatology, Vol. 64, No. 4, 2016.

26- MIZOKAMI M., YOKOSUKA O. and TAKEHARA T.: Ledipasvir and sofosbuvir fixed-dose combination with and without ribavirin for 12 weeks in treatment-naive and previously treated Japanese patients with genotype 1 hepatitis C: An open-label, randomised, phase 3 trial. Lancet. Infect. Dis., 15 (6): 645-53, 2015.

27- HÉZODE C. and BRONOWICKI J.P.: Ideal oral combinations to eradicate HCV: The role of ribavirin. J. Hepatol., 64 (1): 215-25. [64], 2016.

28- SULKOWSKI M.S., GARDINER D.F., RODRIGUEZ-TORRES M, REDDY K.R., HAS SANEIN T. and JACOBSON I.: Daclatasvir plus sofosbuvir for previously treated oruntreated chronic HCV infection. N. Engl. J. Med., 370: 211-21, 2015.

29- KOHLI A., KAPOOR R., SIMS Z., NELSON A., SIDHARTHAN S. and LAM B.: Ledipasvir and sofosbuvir for hepatitis C genotype 4: A proof-of-concept, single-centre, open-label phase 2a cohort study. The Lancet. Infectious Diseases, 15 (9): 1049-54, 2015.

30- BOURLIERE M., LUCIER S., HEZODE C., DORIVAL C., LARREY D., BRONOWICKI J.P. and LEDINGHEN V.: Safety and efficacy of daclatasvir-sofosbuvir in HCV genotype1-mono-infectedpatients. Jan., 66 (1): 39-47. doi:10.1016/j.jhep.2016.08.021. Epub. 2016 Sep. 10, 2016.

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 آنحاء 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 آظهر العديد من الآثار الجانبية الخطيرة بجانب إنخفاض فعالية هذا النظام العلاجى. ولكن فى عام ٢٠١٣، نشآ جيل ثانى من المضادات الفيروسية المباشرة آعطت 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 آظهرت هذه الدراسة سلامة وفعالية النظام العلاجى المتضمن عقار (السوفوسبوفير مع آحد المضادات الفيروسية المباشرة الآخرى مثل الدكلاتاسيفير والليديباسيفير والسيميبرفير) لمدة ١٢ آسبوع آظهر سلامة وفعالية فى الشفاء، كما آظهرت هذه الدراسة آهمية (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 لتآكيد قيمته التنبؤية.