



# Generic Sofosbuvir/Ledipasvir for Treatment of Naïve, Non-Cirrhotic, Easy to Treat Patients with Chronic Hepatitis C Genotype 4: 8 Vs. 12 Weeks of Treatment

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## Abstract

**Background:** 12-week sofosbuvir/ledipasvir combination is approved for the treatment of HCV genotype 4.

**Objectives:** The study aimed to evaluate the safety and efficacy of generic sofosbuvir/ledipasvir for 8 and 12 weeks in easy to treat patients infected with the hepatitis C virus (HCV) genotype 4.

**Methods:** In this prospective randomized study, 40 naïve non-cirrhotic easy to treat patients were randomized to receive 8 or 12 weeks (groups 1 and 2, respectively) of generic ledipasvir/sofosbuvir (MPIviropack-Plus provided by Marcyrl Pharmaceutical Industries). A simple randomization was done using computer-generated random numbers by Microsoft Excel. The primary endpoint was the sustained virological response 12 weeks post-treatment (SVR12).

**Results:** There was no significant difference between the two groups of 8 and 12 weeks of therapy in pre-treatment demographics, laboratory parameters, and viral load. A more significant reduction in liver enzymes was noticed in group 2. No adverse events were recorded. SVR12 was 100% with 8 weeks of generic sofosbuvir/ledipasvir and 95% with 12 weeks of the same regimen.

**Conclusions:** Generic sofosbuvir/ledipasvir for 8 weeks is highly effective with a high rate of SVR12 among naïve non-cirrhotic easy to treat patients with HCV genotype 4 infection. No additional benefit was associated with the extension of the treatment duration to 12 weeks.

**Keywords:** HCV Treatment, Egypt, Generic, Sofosbuvir, Ledipasvir

## 1. Background

In Egypt, the seroprevalence of hepatitis C virus (HCV) infection declined from about 15% in 2008 to 6.3% in 2015 among the studied population (1), with an overall estimated 30% decrease in the HCV prevalence (2). Genotype 4 is responsible for over 90% of infections and the rest of the infections is due to genotype 1 (3, 4). HCV treatment using combinations of directly acting antiviral (DAA) agents has led to a great increase in the number of patients achieving sustained virological response (SVR) rates, reaching up to 90% - 95% and even higher (5).

The sofosbuvir/ledipasvir (SOF/LDV) combination is available in a two-drug fixed-dose tablet containing sofosbuvir 400 mg and ledipasvir 90 mg. It has been recently approved for the treatment of genotypes 1, 4, 5, and 6 as a once-daily 12-week regimen for treatment of naïve non-

cirrhotic patients or patients with compensated cirrhosis (Child-Pugh A) (6). The SOF/LDV combination also provided a chance to consider 8 versus 12 weeks of treatment for genotype 1 infected patients with favorable virological and clinical characteristics (7). The most common adverse events reported with SOF/LDV combination were a headache and fatigue (6).

The use of low-cost generic DAAs was adopted by some countries due to the very high cost of branded versions. Their use was proved a feasible and economical alternative with comparable high SVR12 rates (8, 9).

The "global health sector strategy on viral hepatitis, 2016 - 2021" was recently formulated by The World Health Organization and determined service coverage goals to eliminate hepatitis C infection. This would be achieved through scaling-up of hepatitis C diagnosis and treatment

by 2030 for a coverage of 90% and 80%, respectively, and an 80% decrease in incidence (10).

The National Committee for Control of Viral Hepatitis (NCCVH) in Egypt has started a mass therapeutic program (10) with sofosbuvir-based drug combinations since October 2014 with chronological changes in the used drugs (11-13). Generic DAAs have been used in the Egyptian national treatment program since October 2015 (14). Egypt is on the road to elimination of HCV. It is one of the only ten countries wherein, patients achieving SVR are 5 times more than patients with new infections (15).

## 2. Objectives

The objective of the current study was to assess the safety and efficacy of generic SOF/LDV combination therapy for eight versus 12 weeks in naïve, non-cirrhotic, easy to treat Egyptian patients infected with hepatitis C virus (HCV) genotype 4.

## 3. Methods

This prospective randomized study included 40 Egyptian patients with HCV (genotype 4) infection who were candidates for anti-viral therapy according to the guidelines of the National Committee for Control of Viral Hepatitis (NCCVH) (16) during the period of recruitment (from February 2017 to July 2017). This study was based on a purposive sampling. Patients were randomly divided into two equal groups by simple randomization using computer-generated random numbers by Microsoft Excel. The person performing HCV polymerase chain reaction at the end of the treatment and 12-week post-treatment did not know if this patient had received 8 or 12 weeks of treatment. The person randomizing the patients did not know what the next treatment duration allocation would be. This study included easy to treat patients (11) who were: adults > 18 years of both sexes, viral load of less than 2,000,000 IU/mL, fibrosis stages (Fo-F1-F2) by fibro-scan, naïve to antiviral therapy, those not having cirrhosis, and those having compensated liver biochemical parameters: serum bilirubin  $\leq$  1.2 mg/dL, serum albumin  $\geq$  3.5 g/dL, INR  $\leq$  1.2, and platelet count  $\geq$  150 000 cmm.

The exclusion criteria were patients with advanced fibrosis stages (fibrosis stages F3 and F4) by transient elastography, HBV or HIV co-infection, pregnancy or inability to use effective contraception, inadequately controlled DM (HbA1c of more than 9%), hepatic or extrahepatic malignancy, creatinine clearance of less than 30 mL/min,

breastfeeding, patients with organ transplant or using immunosuppressive drugs, substance abuse, IV drugs, inhaled drugs, and drug-related liver disease.

The patients received the generic form of SOF/LDV combination under the name of "MPIviropack Plus" provided by Marcyrl Pharmaceutical Industries, Cairo, Egypt, that contained a combination of SOF 400 mg and LDV 90 mg. group 1 (20 patients) received generic SOF/LDV daily fixed dose 400/90 mg for 8 weeks only while group 2 (20 patients) received the same treatment for 12 weeks.

The patients were subjected to baseline and follow-up full history taking and clinical examination with a special emphasis on any complications during or after the end of treatment like fatigue, headache, fever, jaundice, and rash. Routine laboratory and radiological investigations were performed at baseline and at the end of therapy to determine complete blood picture, liver biochemical profile (total serum bilirubin, direct and indirect bilirubin, serum albumin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, prothrombin time, and international normalized ratio (INR)), serum creatinine, alfa-fetoprotein (AFP), and abdominal ultrasonography. In addition, quantitative HCV-RNA was conducted by real-time polymerase chain reaction (PCR) (TaqMan probe) ABI 7900 (Thermo Fisher Scientific, Waltham, USA), before the start of treatment, four weeks after the start of therapy, at the end of therapy, and 12 weeks after the end of therapy.

Transient elastography was performed on all patients before treatment. The cutoff values for liver stiffness measurements expressed in Kpa were used in this study according to De Ledinghen and Vergniol (17) as follows: F0: 0 - 5.4 Kpa, F0 - F1: 5.5 - 5.9 Kpa, F1: 6 - 6.9 Kpa, F1 - F2: 7 - 8.7 Kpa, F2: 8.8 - 9.4 Kpa, F3: 9.5 - 12.4 Kpa, F3 - F4: 12.5 - 14.4 Kpa, and F4:  $\geq$  14.5 Kpa.

The study was performed in compliance with the ethical principles of the 1964 Declaration of Helsinki (as revised in Brazil 2013) and its later amendments with GCP guidelines. The study protocol, as well as the informed consent, was approved by the research ethics committee of the Institutional Review Board (IRB) of Cairo University (number N-38 - 2016).

### 3.1. Statistical Methods

Data were coded and entered into SPSS (Statistical Package for the Social Sciences) version 24 software. The data were summarized using mean, standard deviation, median, minimum, and maximum for quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between the two

groups were made using unpaired t test for normally distributed quantitative variables while the non-parametric Mann-Whitney test was used for non-normally distributed quantitative variables. For comparison of serial measurements (pretreatment and end of treatment) for each patient, the paired t test was used (18).

For comparing categorical data, the Chi-square ( $\chi^2$ ) test was performed. The exact test was used instead when the expected frequency was less than five (19). P values of less than 0.05 were considered statistically significant.

#### 4. Results

The demographic and laboratory features of the two studied groups are shown in Table 1. There was no significant difference between the two groups regarding their age, gender, BMI, baseline liver stiffness or laboratory parameters, and viral load. There were no adverse effects recorded during therapy in any of the treated patients.

The follow-up laboratory parameters after treatment revealed no significant change apart from AST and ALT, which showed a significant reduction in the two groups (Table 2). Patients in group 2 who received 12 weeks of therapy showed a more significant reduction in AST and ALT. Regarding the virological response, there were three patients who had positive HCV PCR four weeks after the initiation of therapy, including one patient in group 1 and two patients in group 2. At the end of therapy, all patients in the two groups had negative HCV PCR.

SVR12 was achieved in all patients of group 1 while one patient (5%) in group 2 failed to achieve SVR12 (Table 3). The patient who failed to achieve SVR was a 45-year-old male patient, with a BMI of 22.4. He was not diabetic, hypertensive, smoker, or alcoholic. His liver stiffness measurement was 4.7 KPa (F0) by fibroscan with a baseline viral load of 5007 IU/mL. His HCV RNA at week 4 of treatment and at the end of treatment was negative. HCV RNA 12 weeks after the end of treatment was 35 000 IU/mL.

#### 5. Discussion

Drug price is a considerable obstacle to implementing treatment for chronic hepatitis C with direct-acting antiviral agents (DAAs)-based regimens (20). Gilead and Bristol-Myers Squibb pharmaceutical companies have granted voluntary licenses (VLs) to generic companies to mass produce cheaper generic DAAs that proved to be bioequivalent

to the originator drugs. Mass treatment of chronic hepatitis C with generic DAAs at a low cost is the most hopeful approach to reach the ambitious World Health Organization goals for HCV eradication by 2030 (9).

In the present study, the aim was to assess the response of chronic hepatitis C genotype 4 infected patients to treatment with generic SOF/LDV combination and compare the response rates between eight and twelve weeks regimens. 40 patients were included in the study and were randomized into two groups according to the duration of treatment.

The 8-week course of “MPLiviropack Plus” treatment costs 2200 L. E while the 12-week regimen costs 3300 L. E. The 8-week regimen would be cheaper particularly for patients with no health insurance who have to buy the drugs by their own. In addition, no added benefit was associated with the extension of the duration of treatment to 12 weeks.

In the present study, patients who received 8 weeks of treatment regimen showed a response rate of 100% that is higher than that previously reported among patients with genotype 4 infection. Shiha et al. (21) reported an SVR12 of 95% (41 of 43 patients) in naïve non-cirrhotic Egyptian patients chronically infected with HCV genotype 4 who received SOF/LDV for 8 weeks while SVR12 was 98% (42 of 43 patients) in patients who received the same regimen for 12 weeks.

Naïve, non-cirrhotic, easy to treat patients in our study showed the SVR12 rates after 8 weeks of treatment with SOF/LDV that was higher than the rates previously reported among genotype 1 patients. Kowdley et al. (22) reported SVR12 rates of 94% with 8 weeks of SOF/LDV, 93% with 8 weeks of LDV-SOF plus ribavirin, and 95% with 12 weeks of LDV-SOF in non-cirrhotic genotype 1 infected patients. Curry et al. (23) reported an SVR rate of 95.3% and there was no statistical difference in SVR rates between patients who received 8 and 12 weeks of SOF/LDV combination therapy irrespective of any clinical or virological parameters. In addition, Buggisch et al. (24) revealed that in the 8-week group, 85.1% of the intention-to-treat and 98.3% of the per-protocol patients achieved SVR12 while in the 12-week group, 85.5% of the ITT and 98.1% of the PP patients achieved SVR12. This may be related to the genotype difference compared to our study and that all of our patients were easy to treat with minimal to mild fibrosis stages.

The 8-week treatment regimen with SOD/LDV was also studied on other genotypes. Nguyen et al. (25) conducted a study on patients chronically infected with HCV genotype 6 without cirrhosis or prior treatment failure, as well

**Table 1.** Baseline Characteristics of the Two Studied Groups<sup>a</sup>

	Group 1 (8 Weeks of Generic SOF/LDV)	Group 2 (12 Weeks of Generic SOF/LDV)	P Value
Gender (male/female)	10 (50)/10 (50)	7 (35)/13(65)	0.337
Age (y)	37.65 ± 14.25	40.60 ± 14.14	0.547
BMI	26.04 ± 3.19	27.24 ± 4.79	0.414
Liver stiffness KPa	5.54 ± 1.43	5.35 ± 1.51	0.547
F0	10 (50)	12 (60)	0.302
F1	4 (20)	4 (20)	0.302
F0 - F1	3 (15)	2 (10)	0.302
F1 - F2	3 (15)	0 (0)	0.302
F2	0 (0)	2 (10)	0.302
Diabetes mellitus	2 (10)	1 (5)	1
History of bilharziasis	2 (10)	4 (20)	0.661
White blood cells (10 <sup>3</sup> /cmm)	6.24 ± 1.86	6.77 ± 2.17	0.414
Hemoglobin (gm/dL)	13.75 ± 1.81	13.10 ± 1.63	0.240
Platelet count (10 <sup>3</sup> /cmm)	239.75 ± 46.29	266.35 ± 57.49	0.115
Serum albumin (gm/dL)	4.46 ± 0.42	4.34 ± 0.36	0.380
Total bilirubin (mg/dL)	0.65 ± 0.24	0.54 ± 0.21	0.139
Direct bilirubin (mg/dL)	0.21 ± 0.14	0.21 ± 0.13	0.946
ALT (U/L)	38.25 ± 12.67	41.05 ± 24.81	0.656
AST (U/L)	35.40 ± 9.11	35.30 ± 16.05	0.981
Serum creatinine (mg/dL)	0.73 ± 0.18	0.75 ± 0.23	0.764
INR	1.03 ± 0.05	1.01 ± 0.08	0.319
AFP (ng/mL)	3.62 ± 1.95	3.52 ± 1.35	0.968
Viral load (IU/mL)	363094.62 ± 485807.82	429048.01 ± 505015.62	0.495

<sup>a</sup> Values are expressed as No. (%) or mean ± SD.

**Table 2.** Comparison of Laboratory Data at Baseline and at the End of Treatment in Both Groups<sup>a</sup>

	Group 1 (8 Weeks of Generic SOF/LDV)			Group 2 (12 Weeks of Generic SOF/LDV)		
	Baseline	12W After Treatment	P Value	Baseline	12W After Treatment	P Value
White blood cells (10 <sup>3</sup> /cmm)	6.24 ± 1.86	6.83 ± 2.76	0.244	6.77 ± 2.17	6.88 ± 1.84	0.710
Hemoglobin (gm/dL)	13.75 ± 1.81	13.50 ± 1.91	0.373	13.10 ± 1.63	12.83 ± 2.05	0.192
Platelet count (10 <sup>3</sup> /cmm)	239.75 ± 46.29	241.90 ± 38.91	0.872	266.35 ± 57.49	257.60 ± 60.59	0.466
Serum albumin (gm/dL)	4.46 ± 0.42	4.31 ± 0.32	0.093	4.34 ± 0.36	4.26 ± 0.36	0.297
Total bilirubin (mg/dL)	0.65 ± 0.24	0.67 ± 0.37	0.757	0.54 ± 0.21	0.52 ± 0.17	0.532
Direct bilirubin (mg/dL)	0.21 ± 0.14	0.19 ± 0.10	0.362	0.21 ± 0.13	.19 ± 0.09	0.373
ALT (U/L)	38.25 ± 12.67	20.90 ± 9.68	< 0.001	41.05 ± 24.81	16.13 ± 7.32	< 0.001
AST (U/L)	35.40 ± 9.11	23.60 ± 8.73	0.002	35.30 ± 16.05	17.67 ± 4.13	< 0.001
Serum creatinine (mg/dL)	31.15 ± 12.38	27.70 ± 6.11	0.233	25.70 ± 5.91	26.80 ± 7.30	0.418
INR	0.73 ± 0.18	0.84 ± 0.16	0.102	0.75 ± 0.23	0.70 ± 0.17	0.302
AFP (IU/mL)	1.03 ± 0.05	1.06 ± 0.11	0.379	1.01 ± 0.08	1.00 ± 0.05	0.721

<sup>a</sup> Values are expressed as mean ± SD.

as on patients with cirrhosis and/or prior treatment failure. SVR12 rates were 95.0% for the 8-week group and 95.0% for the 12-week group. Gane et al. (26) conducted another study on patients chronically infected with HCV genotype 2 who were naïve and treatment-experienced and revealed

SVR12 rates of 96% for 12 weeks and 74% for 8 weeks of SOV/LDV.

Regarding the changes in baseline laboratory data in the studied groups, we found a significant improvement in AST and ALT that could be explained by inflammation

**Table 3.** Treatment Response in the Studied Groups<sup>a</sup>

Treatment Response	Group I (n = 20)	Group II (n = 20)
HCV RNA PCR 4 weeks after treatment initiation (negative/positive)	19 (95)/1 (5)	18 (90)/2 (10)
End of treatment	20 (100)	20 (100)
SVR12	20 (100)	19 (95)
Non-SVR12	0 (0)	1 (5)

<sup>a</sup> Values are expressed as No. (%).

regression following treatment. This agrees with different studies that included treatment of different HCV genotypes with DAAs (27-30). On the other hand, there were no significant changes in other laboratory parameters of the patients.

A limitation of our study is the small number of enrolled patients. The sequencing analysis of the virological failure was not done. Thus, no interpretation of the potential NS5A or NS5B resistance-associated substitutions could be made.

In summary, the 8-week treatment regimen of generic SOF/LDV, using two DAAs with distinct viral targets and mechanisms of action, could show a high efficacy in the treatment of naive non-cirrhotic easy to treat chronic HCV genotype 4 infection. For the generalization of the study results to the whole population, there is a need for a high-quality study with large numbers of participants.

#### Footnotes

**Authors' Contribution:** All authors have contributed significantly to finish this work; all authors are in agreement with the content of the manuscript, design of the study: Gamal Esmat, Hend Shousha, performance of management: Karim Akl, Sherif, acquisition of data: Karim Akl, analysis of data: Karim Akl, Hend Shousha, interpretation of data and drafting the article: Hend Shousha, Karim Akl, article revision: Sherif Ragheb, Eman Medhat, Gamal Esmat, final approval of the version: Eman Medhat, Gamal Esmat, article submission: Hend Shousha.

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**Ethical Considerations:** The study was performed in compliance with the ethics principles of the 1964 Declaration of Helsinki (as revised in Brazil 2013) and its later amendments with GCP guidelines. The study protocol, as

well as the informed consent, were approved by the Institutional Review Board (IRB) of Cairo University Research Ethics Committee number N-38-2016.

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