



# Safety and Efficacy of Ledipasvir/Sofosbuvir in the Treatment of Chronic Hepatitis C Virus Infection in Treatment-Naïve Children without and with Comorbidities

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Accepted: 19 June 2022 / Published online: 15 July 2022  
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## Abstract

**Background** Chronic hepatitis C virus (HCV) infection represents a crucial health problem in children that greatly influences their quality of life. Many efforts have been directed toward investing in effective drugs with a high safety profile and oral administration for better compliance.

**Objectives** This study aims to assess the safety of a fixed-dose combination of ledipasvir/sofosbuvir plus drug efficacy and sustained virologic response (SVR) at 12 weeks after treatment discontinuation.

**Method** One tablet (90 mg ledipasvir, 400 mg sofosbuvir) was administered to treatment-naïve children aged 12–18 years weighing at least 35 kg with chronic HCV infection for 6 months, genotype 4. Patients were divided into 2 groups, (1) without comorbidities (24 patients) and (2) with comorbidities (26 patients).

**Results** At the end of the therapy, all patients (100%) had SVR and a significant reduction of liver enzymes with mild tolerable side effects.

**Conclusion** Ledipasvir/sofosbuvir fixed-dose combination is a safe and highly effective therapeutic option in Egyptian children aged  $\geq 12$  years, with chronic HCV infection, genotype 4, either without or with comorbidities.

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## Key Points

Pediatric HCV patients with comorbidities such as cancer, epilepsy, hemophilia, thalassemia, and nephrotic syndrome are neglected.

Pediatric HCV infection has an aggressive course due to associated chronic disease or medications received.

Ledipasvir–sofosbuvir fixed-dose combination is safe and effective in this special population.

## 1 Introduction

Hepatitis C virus (HCV) infection in children continues to be a serious public health concern, with an estimated global prevalence of 0.13%, equating to 3.26 million viremic children worldwide. Pakistan, China, India, and Nigeria accounted for more than half of all viremic HCV infections

[1]. Hepatitis C virus antibodies and HCV RNA were found in 0.4 % and 0.2 % of Egyptian children aged 1–14 years, respectively, rising to 1 % and 0.8 % in teenagers aged 15–19 years [2].

Hepatitis C virus infection in children is frequently asymptomatic and has a slower progression with an unpredictable histological course than in adults [3]. Cirrhosis is documented in 1–2% of persistently infected adolescents and children, including decompensation, even though histology may show a normal liver [4], and there are few case reports of hepatocellular carcinoma [5]. Advanced liver disease and decompensated cirrhosis have been diagnosed in children aged as young as 3 years and as early as 1 year after infection [6]. Patients with longer follow-up and infection duration have more evidence of disease progression, and progression is more likely 10 years after the start of infection [7]. In addition, HCV infection has been linked to poor quality of life and cognitive impairment in children [8, 9].

Thanks to the development of direct-acting antivirals (DAAs), chronic hepatitis C infection has been transformed from a condition requiring complex therapies with unsatisfactory outcomes to one that can be easily treated with few adverse effects [10]. In 2017, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) approved the use of the fixed-dose combination of ledipasvir/sofosbuvir and also the combination of sofosbuvir and ribavirin for treatment of adolescents (aged 12–17 years or weighing > 35 kg) with chronic HCV genotype 1, 4, 5, and 6 and genotype 2 and 3 infections, respectively [11].

Recently, the HCV recommendation panel of the 2019 American Association for the Study of Liver Diseases and Infectious Diseases Society of America supported DAA therapy for all children and adolescents (aged  $\geq 3$  years) with HCV infection. Age, treatment status, indications of cirrhosis, and HCV genotype all play a role in determining which medication combination is best for the patient: ledipasvir/sofosbuvir and sofosbuvir/ribavirin for 12 weeks are approved for those aged  $\geq 3$  years in HCV genotypes 1, 4, 5 and 6, and genotypes 2 and 3, respectively. In March 2020, the FDA expanded the approval of sofosbuvir/velpatasvir for 12 weeks to children aged 6 to < 18 years with any genotype. Also, the combination of glecaprevir/pibrentasvir was approved for children aged  $\geq 3$  with any genotype for a duration of 8 weeks [12].

Comorbidities such as hematological illnesses with iron overload, obesity, cancer, and viral co-infections such as human immunodeficiency virus (HIV) and hepatitis B virus (HBV) might hasten the development of hepatic fibrosis in adolescents and children [4]. For example, many patients with inherited blood disorders have been infected with HCV because of the many transfusions they receive. Transfusion-associated liver iron overload leads to the advancement of liver fibrosis and exposure to complications of chronic liver disease, including cirrhosis, end-stage liver disease, and

hepatocellular carcinoma [13]. In these patients, pegylated interferon (pegIFN) and ribavirin were contraindicated because of the risk of ribavirin-associated anemia [14].

Hepatitis C virus infection is a neglected disease in patients with cancer [15]. It is more aggressive in these patients because of the concurrent use of cytotoxic chemotherapy, which increases the risk of fibrosis progression, early cirrhosis, and hepatocellular carcinoma [16]. Case studies have reported the need for dosage reduction or cessation of chemotherapy in 80 % of pediatric acute leukemia cases who are anti-HCV positive due to hepatotoxicity. Safety and effectiveness data among immunosuppressed populations are limited, despite the recent clearance of DAA for use in pediatrics [17]. The current study was conducted just after the beginning of the Egyptian protocol for treating chronic HCV infection in pediatrics to confirm the high efficacy and safety profile of sofosbuvir/ledipasvir in the Delta region. We emphasize in this study the use of DAA in chronic HCV pediatric populations with comorbidities because of the above-mentioned aggressive natural history and complications of the associated chronic illness and medications with limited research on these individuals.

## 2 Patients and Methods

This is a prospective therapeutic clinical trial study (over 18 months from March 2018 to August 2019) that evaluated the safety and efficacy of combined sofosbuvir/ledipasvir in treating chronic HCV infection in treatment-naïve children.

Fifty treatment-naïve children with chronic HCV genotype 4 infection diagnosed by positive HCV RNA PCR test [18] were recruited from the gastroenterology and hepatology outpatient clinic at Mansoura University Children's Hospital (MUCH). All patients and their parents were informed about the safety, efficacy, and adverse effects of the drugs before the start of the study. Written informed consent was obtained from all parents or legal guardians of the included patients. All were aged between 12 and 18 years or weighed at least 35 kg, with chronic HCV infection  $\geq 6$  months, without or with compensated cirrhosis, and no fibrosis. Those with certain comorbidities, such as decompensated heart failure [19], severe renal impairment [glomerular filtration rate (GFR) < 30] [20], uncontrolled diabetes mellitus (DM) [21], concomitant HBV [22] or HIV infection [23] and those who were maintained on beta-blockers or amiodarone were excluded.

### 2.1 Study Groups

Patients were divided into two groups:

- The group without comorbidities included 24 patients (16 males, 8 females).

- The group with comorbidities included 26 patients (20 males, 6 females).

The group with comorbidities included 1 patient with ankylosing spondylitis, 7 patients with thalassemia, 1 patient with hemophilia A, 14 patients with previously treated malignancies (5 had leukemia, 4 had lymphoma, 3 had medulloblastoma, 1 had Langerhans cell histiocytosis, and 1 had retinoblastoma), 1 patient had nephrotic syndrome and 2 had epilepsy.

## 2.2 Methods

Relevant data from all included patients were obtained, including risk factors for HCV infection, date and route of acquisition, and medications, including previous antiviral therapy. Hepatitis C virus genotyping was done before treatment, revealing GT 4 in all included patients. Fibroscan, which was done for all patients and showed no fibrosis. Before treatment, a basic electrocardiogram (ECG) and abdominal ultrasonography were performed. Concomitant HBV infection was excluded by HBsAg [24] and anti-HBc antibody for fear of fulminant hepatitis B infection [25]. Human immunodeficiency virus screening was done prior to treatment. Basic investigations were conducted prior to therapy, including: complete blood count (CBC), serum creatinine (SCr), blood urea nitrogen (BUN), random blood glucose (RBG), and liver function tests (LFT), including serum albumin, total and direct bilirubin, and international normalized ratio (INR). For 12 weeks, all patients were given a fixed-dose combination of ledipasvir–sofosbuvir [Harvoni “90 mg ledipasvir, 400 mg sofosbuvir”] orally once daily at a fixed time with or without food. Regular visits were arranged at the pediatric hepatology unit at 4, 8, and 12 weeks with easy access to the treating physician if any urgent problem arose between the visits. Some patients with comorbidities were maintained on medications. Drug interactions were checked using the application (Liverpool HEP ichart), and no interactions were found before or during the treatment. At every visit, CBC, SCr, BUN, RBG, and LFTs were checked. Adverse events (after excluding other possible causes) were reported for the drug’s safety profile.

Regarding the efficacy of the drug, HCV-RNA was assessed by quantitative real-time PCR [18] at 4 weeks and after the end of the treatment course (12 weeks).

## 2.3 Statistical Analysis

The SPSS software (Statistical Package for the Social Sciences, version 24), was used for data processing. Continuous variables were presented as mean  $\pm$  standard deviation (SD) for parametric data and median and inter-quartile range (IQR) for non-parametric data. The study groups were compared using Student *t*-test for parametric data and Mann-Whitney test for non-parametric data, while paired groups were compared by the paired *t*-test (parametric) and Wilcoxon signed rank test (nonparametric). The *p* values less than 0.05 were considered significant.

## 3 Results

The 50 children included were all aged 12–18 years except 4 patients who were aged less than 12 years but weighed more than 35 kg (1 without and 3 with comorbidities). As shown in Table 1, there was no significant difference between either group with regard to age or sex distribution. At the end of treatment, we found that only 2 patients had mild hepatomegaly, and both had thalassemia. In both groups, 10 patients had elevated liver enzymes at the start of the treatment compared to only 4 patients at the end of the treatment; 2 from 10 patients (1 without comorbidity and the other with) showed improved INR. The reduction of liver enzymes reached statistical significance, but INR did not. On the other hand, total bilirubin increased, which can be explained by non-compliance with ursodeoxycholic acid by some patients (Tables 2 and 3). Platelet count decreased in HCV patients with comorbidities but was still in the normal range, so this may be related to the chronic conditions of the patients (Table 3).

A comparison between patients without comorbidities and those with comorbidities was made before and at the end of the treatment. Pretreatment comparison showed no statistical difference except for hemoglobin (HB) and INR;

**Table 1** Demographic data of the studied groups

Demographic data	Patients without comorbidities ( <i>n</i> = 24)	Patients with comorbidities ( <i>n</i> = 26)	Test of significance	<i>p</i> value
Age/years				
Mean $\pm$ SD	15.01 $\pm$ 1.84	14.65 $\pm$ 2.15	<i>t</i> = 0.791	0.433
Gender				
Male	16 (66.7 %)	20 (76.9 %)	$\chi^2$ = 0.651	0.420
Female	8 (33.3 %)	6 (23.1 %)		

**Table 2** Comparison between laboratory parameters before and after end of treatment in patients without comorbidities

Laboratory investigations	Group of patients without comorbidities		Test of significance	p value
	Pretreatment (n = 24)	End of treatment (n = 24)		
TLC (k/ $\mu$ L), median (IQ)	6 (4.47–7.15)	6.55 (5.30–7.50)	Z = 1.03	0.304
HB (g/dL), mean $\pm$ SD	13.11 $\pm$ 1.55	13.06 $\pm$ 2.05	t = 0.266	0.793
Plt (k/ $\mu$ L), median (IQ)	263.5 (194–295.5)	272 (218–298)	Z = 0.243	0.808
ALT (U/mL), median (IQ)	42.50 (26–64.75)	20 (18.00–25.75)	Z = 4.19	< 0.001*
AST (U/mL), median (IQ)	41.5 (34–53.75)	24 (21–27.75)	Z = 4.28	< 0.001*
Albumin (gm/dL), mean $\pm$ SD	4.79 $\pm$ 0.55	4.67 $\pm$ 0.43	t = 0.960	0.347
TSB (mg/dL), median (IQ)	0.65(0.60–0.70)	0.80 (0.62–1)	Z = 2.29	0.022*
INR, mean $\pm$ SD	1.01 $\pm$ 0.04	1.00 $\pm$ 0.02	t = 0.81	0.426
Cr (mg/dL), mean $\pm$ SD	0.80 $\pm$ 0.13	0.75 $\pm$ 0.16	t = 1.135	0.268
RBG (mg/dL), median (IQ)	96 (90.25–105.75)	88 (81.75–93)	Z=1.93	0.065

ALT alanine aminotransferase, AST aspartate aminotransferase, Cr creatinine, HB hemoglobin, INR international normalized ratio, IQ interquartile (1st Q–3rd Q), Plt platelets, RBG random blood sugar, t paired t-test, TLC total leucocytic count, TSB total serum bilirubin, Z Wilcoxon signed rank test

\*Significant  $p \leq 0.05$

this was explained by the chronic situation of patients with comorbidities (Table 4). End of treatment comparison showed no statistical difference between groups (Table 5).

All adverse effects and frequencies observed among our patients were summarized in Table 6 to determine the drug's safety profile. The most encountered adverse effects were headaches, drowsiness, fatigue, abdominal pain, nausea, vomiting, chest pain, and diarrhea. Headache was the most common side effect observed in 24 % of cases, followed by drowsiness in 18 %, and fatigue in 12 %.

Assessment of HCV RNA by real-time PCR was performed one and three months after the end of therapy to assess drug efficacy. It was reported that all included patients turned negative after one month, and all had SVR. This indicates 100 % efficacy of the drug.

## 4 Discussion

The current study evaluated the safety and efficacy of a combined sofosbuvir/ledipasvir regimen in children with chronic HCV, genotype 4 infections. Our patients who received 12 weeks of a single daily tablet of ledipasvir/sofosbuvir (90/400 mg) showed statistically significant improvement in laboratory parameters of liver function, such as a decline in the levels of liver enzymes ALT and AST in both groups.

The most common adverse effects observed among our patients were headache, drowsiness, and fatigue. A few patients complained of nausea, vomiting, chest pain, and abdominal pain. Fortunately, most documented side effects were transient during the first two weeks of therapy and were well tolerated by those affected. None required drug discontinuation. Eleven patients without comorbidity and 12 with

comorbidities did not experience side effects or discomfort. Ledipasvir/sofosbuvir is a safe and well-tolerated drug, similar to that observed in adolescents in other studies [26][26]. A systematic review of a meta-analysis from 2020 showed that headache was the most common side effect in children and adolescents (19.9 %), followed by fatigue (13.3 %) [28].

After assessing HCV RNA by PCR one and three months after the end of protocol therapy, it was clear that SVR was achieved in 100 % of our patients in both groups. This agrees with another Egyptian study published in 2018, which included 40 children (associated comorbid conditions in 27 patients) with chronic HCV infection genotype 4 and reported an overall SVR-12 rate in 100 % of cases with a reduction in liver enzymes and mild adverse effects. The age and weight criteria in the included children was the same as the current study. However, they included both treatment-naïve and treatment-experienced patients [29].

Another multicenter study in 2017 concluded that use of a combination tablet of 90 mg ledipasvir and 400 mg sofosbuvir once daily for 12 weeks achieved SVR in 98 % of patients. The two patients who did not achieve SVR were lost during follow-up. The most observed adverse events were headache (27 % of patients), diarrhea (14 %), and fatigue (13 %). No serious adverse events were reported. The study included adolescents aged between 12 and 17 years but with genotype 1 [26].

Similar results were reported from a prospective multicenter study on chronic HCV, genotype 4 patients, with SVR-12 observed in 142/144 patients (99 %) and minimal tolerable adverse effects [27].

Another study in 2019 reported 100 % efficacy of the same drug regimen in adolescents. However, abdominal pain was the most common side effect, unlike our study, where the headache was the most common [30].

**Table 3** Comparison between laboratory parameters before and after end of treatment in patients with comorbidities

Laboratory investigations	Group of patients with comorbidities		Test of significance	p value
	Pretreatment (n = 26)	End of treatment (n = 26)		
TLC (k/ $\mu$ L), median (IQ)	7.25(5.50–9.45)	7.3 (5.27–9.10)	Z = 0.350	0.726
HB (g/dL), mean $\pm$ SD	11.75 $\pm$ 2.21	11.87 $\pm$ 2.66	t = 0.469	0.643
Plt (k/ $\mu$ L), median (IQ)	294.5 (220.25–294.5)	260 (218.5–327)	Z = 2.07	0.038*
ALT (U/mL), median (IQ)	37.5 (29.75–57)	19.50 (17–21.50)	Z = 3.59	< 0.001*
AST (U/mL), median (IQ)	31.5 (26.75–60)	23.5 (18–28.5)	Z = 4.08	< 0.001*
Albumin (gm/dL), mean $\pm$ SD	4.75 $\pm$ 0.86	4.46 $\pm$ 0.65	t = 1.89	0.070
TSB (mg/dL), median (IQ)	0.60 (0.50–0.72)	0.90 (0.77–1)	Z = 2.17	0.03*
INR, mean $\pm$ SD	1.06 $\pm$ 0.08	1.03 $\pm$ 0.08	t = 1.10	0.282
Cr (mg/dL), mean $\pm$ SD	0.78 $\pm$ 0.17	0.74 $\pm$ 0.25	t = 0.881	0.387
RBG (mg/dL), median (IQ)	90.50 (75.50–98.25)	84 (72.75–90)	Z = 1.98	0.058

ALT alanine aminotransferase, AST aspartate aminotransferase, Cr creatinine, HB hemoglobin, INR international normalized ratio, IQ interquartile (1st Q–3rd Q), Plt platelets, RBG random blood sugar, t paired t-test, TLC total leucocytic count, TSB total serum bilirubin, Z Wilcoxon signed rank test

\*Significant  $p \leq 0.05$

An Egyptian study carried out in 2019 included 157 patients randomly assigned to two groups according to the duration of therapy: one group for 8 weeks (73 patients) and the second group for 12 weeks (84 patients). Patients had the same age and weight criteria as in our but were either treatment-naïve or experienced. Sustained virologic response-12 was 98.6 % in patients treated for 8 weeks and 97.6 % in patients treated for 12 weeks. In all patients, no serious adverse effects led to treatment discontinuation, death, or hepatic decompensation [31].

The same drug regimen was applied to a cohort of treatment-naïve patients chronically infected with HCV, with various genotypes 1a, 1b, or 4, with or without cirrhosis. All patients exhibited SVR 12 weeks after completion of treatment with minimal side effects reported [32].

Further studies that were carried out on younger age groups, 3–6 years and lighter weights (< 35 kg), revealed similar safety and efficacy. They used a combination tablet of 45 mg ledipasvir and 200 mg sofosbuvir; the efficacy was similar between 8 and 12 weeks of therapy, with 100 % SVR-12 rates of 100 %. Nonspecific side effects were observed in all patients [33].

A recent prospective study that included 30 treatment-naïve children without cirrhosis aged 4–10 years with chronic HCV infection revealed SVR-12 in 100 % of cases after a short 8-week course, with minimal side effects [34].

Schwartz et al in 2020 conducted a multicenter study on patients aged 3–6 years with chronic HCV infections, genotypes 1, 3, 4, 5, or 6. The duration of treatment was 12 weeks for all patients except those with cirrhosis secondary to genotype 1 infection who received treatment for 24 weeks. Patients received weight-based doses of ledipasvir/

sofosbuvir fixed-dose combination granules once daily. Overall, 97 % of patients achieved SVR-12 with mild side effects [35].

There are several studies like ours that specifically target the population of chronic HCV with comorbidities. Fourteen patients with thalassemia who had chronic HCV genotype 3 and were treatment-naïve without cirrhosis received sofosbuvir 400 mg/daclatasvir 80 mg daily for 12 weeks. All patients had achieved 100 % SVR, with substantial reductions in liver enzymes [36]. Makhlof et al recruited adolescents with and without hematological disorders who had chronic HCV and received sofosbuvir 400 mg/ledipasvir 90 mg daily for 12 weeks. All patients attained SVR-12 100 % [37]. Many studies performed on adults diagnosed with chronic HCV with blood disorders showed the efficacy and safety of DAA [13, 38, 39].

Patients with malignancies show ALT flares during chemotherapy and have been associated with more rapid liver disease progression and a higher risk of malignancy relapse due to chemotherapy interruption. Jakhar et al reported a case of an HCV-infected child with acute leukemia treated with sofosbuvir/velpatasvir simultaneously with the chemotherapy regimen. The child tolerated the full dose of chemotherapy along with DAA for 12 weeks and was in remission with SVR [17]. An Egyptian study had recruited patients aged 12–18 years with chronic HCV genotype 1 or 4 infection receiving chemotherapy for hematological malignancies who were given sofosbuvir/ledipasvir (400 mg/90 mg) once daily for 12 weeks. All patients completed treatment and achieved SVR-12, 100 % [40]. Another Egyptian prospective, uncontrolled, open-label multicenter study recruited 20 children infected with chronic HCV, genotype 4, who had

**Table 4** Comparison between patients without comorbidities and patients with comorbidities (pretreatment) regarding laboratory investigations

Laboratory investigations	Pretreatment ( <i>n</i> = 53)		Test of significance	<i>p</i> value
	Patients without co morbidities ( <i>n</i> =24)	Patients with comorbidities ( <i>n</i> = 26)		
TLC (k/ $\mu$ L), median (IQ)	6 (4.47–7.15)	7.25 (5.50–9.45)	Z=1.90	0.057
HB (g/dL), mean $\pm$ SD	13.11 $\pm$ 1.55	11.75 $\pm$ 2.21	<i>t</i> =2.48	0.016*
Plt (k/ $\mu$ L) median (IQ)	263.5 (194–295.5)	294.5 (220.25–294.5)	Z=1.69	0.091
ALT (U/mL), median (IQ)	42.50 (26–64.75)	37.5 (29.75–57)	Z=0.19	0.846
AST (U/mL), median (IQ)	41.5 (34–53.75)	31.5 (26.75–60)	Z=0.60	0.547
Albumin (gm/dL), mean $\pm$ SD	4.79 $\pm$ 0.55	4.75 $\pm$ 0.86	<i>t</i> =0.22	0.825
TSB (mg/dL), median (IQ)	0.65 (0.60–0.70)	0.60 (0.50–0.72)	Z=0.77	0.442
INR, mean $\pm$ SD	1.01 $\pm$ 0.04	1.06 $\pm$ 0.08	<i>t</i> =2.32	0.025*
Cr (mg/dL), mean $\pm$ SD	0.80 $\pm$ 0.13	0.78 $\pm$ 0.17	<i>t</i> =0.25	0.801
RBG (mg/dL), median (IQ)	96 (90.25–105.75)	90.50 (75.50–98.25)	Z=1.01	0.319

ALT alanine aminotransferase, AST aspartate aminotransferase, Cr creatinine, HB hemoglobin, INR international normalized ratio, IQ interquartile (1st Q–3rd Q), Plt platelets, RBG random blood sugar, *t* paired t-test, TLC total leucocytic count, TSB total serum bilirubin, Z Wilcoxon signed rank test

\*Significant  $p \leq 0.05$

been in continuous complete remission from leukemia and lymphoma for at least one year. All patients were treated with combined sofosbuvir/daclatasvir for 12 weeks, and all achieved 100 % SVR-12 [41].

## 5 Limitations

The limitations of our study are the relatively small number of patients and the short-term follow-up duration. The patients with comorbidities are a large population and should be divided into subgroups according to their chronic disease to study each special population. Further long-term follow-up studies for adolescents are recommended to observe rare side effects of the new antiviral drugs and to detect the expected high risk of reinfection in the setting of horizontal transmission.

## 6 Conclusion

Treatment with ledipasvir/sofosbuvir fixed-dose combination of one tablet (90 mg ledipasvir, 400 mg sofosbuvir) was well tolerated in Egyptian children and adolescents aged 12 to 18 years or weighing at least 35 kg with treatment-naïve, chronic HCV infection genotype 4 either with or without underlying chronic disease and it achieved 100 % SVR-12 with negligible side effects.

The World Health Organization (WHO) has targeted the eradication of hepatitis C by 2030, as a public health issue [42]. Unfortunately, access to anti-HCV drugs will be

vital in low- and middle-income countries, such as Egypt, where the virus is most widespread, to achieve this target [1]. A micro-elimination approach in pediatric patients with comorbidities may be a strategy. These individuals may have a high prevalence rate, especially in resource-limited settings, and are more prone to spread infection through nosocomial transmission and are at risk for consequences that develop more rapidly [40].

## Declarations

**Funding** Open access funding provided by The Science, Technology & Innovation Funding Authority (STDF) in cooperation with The Egyptian Knowledge Bank (EKB).

**Conflicts of interest** Othman AbouBakr, Mohammed Ezz El Regal, Amr Ali Sarhan, Maysaa El Sayed Zaki, and Ahmed Noaman have no relevant financial or non-financial interests to disclose.

**Availability of data and material** The data presented in this study are available on request from the corresponding author.

**Code availability** Not applicable.

**Authors' contributions** All share the idea, concept, and design in addition of Othman AbouBakr: performed the clinical trial, procedures, and writing. Amr Ali Sarhan: guidance, supervision, and revision of the article. Mohammed Ezz El Regal: shared concept, design of the study, and revision of the article. Maysaa El Sayed Zaki: follow-up materials and equipment and review of laboratory results. Ahmed Noaman: performed the clinical trial, procedures, and writing.

**Ethics approval** This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Mansoura University-Faculty of Medicine (Date 16/12/2017/ No MD/17.11.92)."

**Table 5** Comparison between patients without comorbidities and patients with comorbidities (end of treatment) regarding laboratory investigations

Laboratory investigations	End of treatment ( <i>n</i> = 53)		Test of significance	<i>p</i> value
	Patients without comorbidities ( <i>n</i> = 24)	Patients with comorbidities ( <i>n</i> = 26)		
TLC, median (IQ)	6.55 (5.30–7.50)	7.3 (5.27–9.10)	<i>Z</i> =1.17	0.239
HB, mean ± SD	13.06 ± 2.05	11.87 ± 2.66	<i>t</i> =1.75	0.086
Plt, median (IQ)	272 (218–298)	260 (218.5–327)	<i>Z</i> =0.068	0.946
SGPT, median (IQ)	20 (18.00–25.75)	19.50 (17–21.50)	<i>Z</i> =0.887	0.375
SGOT, median (IQ)	24 (21–27.75)	23.5 (18–28.5)	<i>Z</i> =0.389	0.697
Albumin, mean ± SD	4.67 ± 0.43	4.46 ± 0.65	<i>t</i> =1.27	0.211
TSB, median (IQ)	0.80 (0.62–1)	0.90 (0.77–1)	<i>Z</i> =0.91	0.365
INR, mean ± SD	1.00 ± 0.02	1.03 ± 0.08	<i>t</i> =1.83	0.074
Cr, mean ± SD	0.75 ± 0.16	0.74 ± 0.25	<i>t</i> =0.192	0.848
RBG, median (IQ)	88 (81.75–93)	84 (72.75–90)	<i>Z</i> =1.33	0.191

*ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *Cr* creatinine, *HB* hemoglobin, *INR* international normalized ratio, *IQ* interquartile (1st Q–3rd Q), *Plt* platelets, *RBG* random blood sugar, *t* paired t-test, *TLC* total leucocytic count, *TSB* total serum bilirubin, *Z* Wilcoxon signed rank test

\*Significant *p* ≤ 0.05

**Table 6** Frequency of reported side effects of ledipasvir/sofosbuvir in all included patients

Symptom	Number of patients	Percentage (%)	Week of maximum frequency
Asthenia/Fatigue	6	12	2
Headache	12	24	1
Nausea	4	8	2
Sleepy	5	1	1
Drowsiness	9	18	1
Abdominal pain	5	1	1
Vomiting	2	4	1
Chest pain	1	2	2

**Consent to participate** Written informed consent was obtained from the parents of the patients.

**Consent for publication** Not applicable.

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