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Efficacy and Safety of Generic (Velpatasvir containing regimen) among Adult Chronic HCV Patients Non-responders to Treatment by Sofosbuvir Plus Daclatasvir Regimen in Egypt

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KEY WORDS

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ABSTRACT

Hepatitis C is caused by the hepatitis C virus. Various treatments for hepatitis C were ineffective before the use of direct-acting antivirals (DAAs). DAA has few (negative) adverse effects and high sustained virologic response rate (SVR12).

The aim of this study was to investigate the efficacy and safety of (Velpatasvir-containing regimen) in adult chronic HCV patients unresponsive to Sofosbuvir plus Daclatasvir in Egypt. Patients were assessed clinically and laboratory at the baseline before beginning treatment regimen and monitored clinically and laboratory weekly in the follow up visits for 12 weeks, we report the adverse events t for the safety of the drug. At 12 weeks after treatment, RT-PCR was used to evaluate efficacy. A total of 102 patients. The average age was 55.64 ± 11.13 years old, with (87.3%) male and (12.7%) female. Most patients were treated with SOF+DAC for 3 months 72 (70.6%) while, 30 patients (29.4%) were treated with SOF+DAC+RBV for the same duration. SOF/VEL/VOX therapy had no adverse side effects. The SVR12 rate is 97%. In patients who failed Sofosbuvir plus daclatasvir combination therapy, this study found that combination therapies containing velpatasvir are effective and safe for treating HCV in Egypt.

Introduction

Viral hepatitis is a global health problem that infects millions of people every year **(Jefferies *et al.*, 2018)**. Viral hepatitis is considered a blood-borne infection that affects particularly susceptible individuals; in developing countries **(Jefferies *et al.*, 2018; Obeagu *et al.*, 2018)**.

The World Health Organization (WHO) reported 290,000 deaths from HCV alone, either from cirrhosis or from HCC; worldwide **(WHO, 2022)**. On the other hand, 170 million people mean an HCV virus pandemic; worldwide **(Lauer and Walker, 2001**).

Oral antivirals (DAAs) are used to treat HCV infection. More than 85% of patients treated with different DAA regimens in all six major genotypes were cleared of HCV infection **(Zoratti *et al.*, 2020)**.

In May 2018, both the FDA (Food and Drug Administration) and the EMA (European Medicines Agency) approved 13 direct-acting antivirals (DAAs) for the treatment of HCV. Formerly, HCV was treated with pegylated interferon and ribavirin **(El-Akel *et al.*, 2017)**. Unfortunately, a bad result was attained **(El Raziky *et al.*, 2013)**.

In individuals without cirrhosis or compensated (Child-Pugh A) cirrhosis, SOF/VEL/VOX is recommended for the treatment of chronic (HCV) infection when a previous regimen (protease inhibitor and/or NS5A inhibitor) has failed for HCV genotype 1: 6 **(Bourlière *et al.*, 2017).**

Subjects and Methods

Study design

This prospective cohort study included 102 chronic HCV (HCV-RNA positive) patients who failed to respond to treatment with (sofosbuvir plus daclatasvir) combination therapy from the liver center at El-fayoum health insurance from January 2020 to March 2022. These patients were eligible for non-responders' treatment under the guidelines set by the National Committee for Control of Viral Hepatitis (NCCVH), which was founded by the Egyptian Ministry of Health and Populations in September 2019.

The study was ethically approved by Fayoum University Supreme Committee for Scientific Research Ethics (FU-SCSRE) and was obtained under code no EC 2143, General Administration of Clinical Research in the General Authority for Health Insurance (HIO) and Scientific Research Ethics Committee at The Egyptian Ministry of Health and Populations (MOHP).

The inclusion criteria were adult patients (both genders) ≥18 years old with -(HCV-RNA positive) PCR after

treatment by first-line DAA drug, mainly (sofosbuvir /daclatasvir). the exclusion criteria were pregnant patients or inability to use effective contraception, clinically proven HCC, except for those with 6 months after intervention aiming to cure with no evidence of activity by dynamic imaging (CT or MRI), or having other metastasis except after two years of disease-free interval were excluded from the study as well as patients with History of allergy to one of the components of the study drug and Hepatitis B virus-infected patients.

The primary outcome was the proportion of patients who had a sustained virological response, or SVR12, defined as persistently undetectable HCVRNA at week 12 following treatment. The secondary outcome was adverse events related to the treatment.

Measurements

Patients with a full medical history and complete clinical assessment, with a focus on previous HCV treatment duration and the type of treatment as well as associated comorbidities and drugs were included.

All the patients before enrolment were exposed to the following laboratory tests conducted at baseline investigations: complete blood count (CBC), fast blood sugar, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, serum albumin, serum hepatitis bs antigen (HBsAg),serum international normalized ratio (INR), glycated hemoglobin (HBA1C), serum creatinine and alpha-fetoprotein A quantitative measurement of HCV-RNA was performed by real-time PCR -abdominal ultrasound was performed to examine the liver and detect hepatocellular carcinoma (any detected HCC were excluded).

All patients received a fixed-dose combination tablet of (400 mg of sofosbuvir, 100 mg of velpatasvir, and 100 mg of voxilaprevir). One tablet was taken orally, once daily with food for 12 weeks.

Monthly follow-up visits were performed, which included a medical examination and laboratory tests such as CBC and creatinine.

At each visit, all patients were evaluated for clinical side effects. Hematological side effects were assessed at weeks 4, 8 of therapy, at 4-week intervals thereafter, One side effect that was reasonably related was noted. Records of serious adverse events or patient hospitalizations.

Determination of the efficacy of VOSEVI administration was done through:

1. Performing the recommended quantitative testing (HCV-RNA) PCR before starting treatment, after 12 weeks from the end of a treatment regimen.

2. Determining whether the patient had achieved SVR.
3. Undetectable (HCV-RNA) level at 12 weeks after completing therapy was referred as SVR12.

Statistical analysis

Data were expressed as numbers (No), percentage (%), mean ($\bar{x}$) and standard deviation (SD). Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test the normality of different variables. A repeated-measures ANOVA test (with Bonferroni correction) and Mauchly's test as a test of sphericity were used to compare three or more consecutive measurements within the same group of quantitative variables. Assumed sphericity was used for normally distributed data, while Greenhouse-Geisser was used for non-normally distributed data. A 2 Advances in Virology and two-sided p-value; 0.05 was considered statistically significant. Statistical analysis was performed using the Statistical Package for the Social Sciences version 28 (SPSS Inc. Released 2022. IBM SPSS Statistics for Windows, version 23.0, Armnok, NY: IBM Corp.)

Results

Baseline demographic and clinical characteristics (N =102)

This study was conducted on 102 adult chronic HCV patients (HCV-RNA positive) who were non-responders to treatment by sofosbuvir plus daclatasvir combination regimen.

Table (1): Baseline demographic and clinical characteristics

Variables		All patient N=102		
Age (year)		Min	Max	Mean, S.D
		32	76	55.64±11.13
		(N)		%
Sex	Male	89		87.3%
	Female	13		12.7%
D.M		11		10.8%
Non-Diabetic		91		89.2%
HTN		20		19.6%
D.M+HTN		10		9.8%
Liver in ultrasound	Normal	18		17.6%
	Bright liver	20		19.6%
	Cirrhosis	14		13.7%
	Hepatomegaly	10		9.8
	Chronic liver disease	40		39.2%
Previous treatment	Sofosbuvir + Daclatasvir for 3 months	72		70.6%
	Sofosbuvir + Daclatasvir + Ribavirin for 3 months	30		29.4%

According to Table (2), among 102 HCV non-responders, HCV PCR mean is 5.23. The baseline mean hemoglobin is 13.8 and baseline mean for white blood cells is 6.12. Moreover, baseline mean platelets are 172.95. Regarding AST, and ALT means in the baseline, they are 47.82, and 54.64; respectively. The baseline mean total bilirubin is 0.85. The baseline mean for fasting blood sugar for all patients is 112.21 and for serum creatinine is 0.93.

Table (2): Baseline biological characteristics of HCV non-respondents patients

Variables		Pretreatment patients count (%)
HCV PCR (log10)		5.23 (0.86)
HBsAg	**YES**	0 (0.0)
	NO	102 (100.0)
HGB[a] (g/dl)		13.81±1.45*
WBCs[a] (×10 ^{3}/mm^3)		6.12±1.98
PLT[a] (×10 ^{3}/mm3)		172.95±55.712
ALT[a] (ULN:50 U/L)		54.64±35.58
AST[a] (ULN:50 U/L)		47.82±33.52
Bilirubin[a] (mg/dl)		0.85±0.47
FBS (mg/dl)		112.21±49.87
Albumin[a] (g/dl)		4.17±0.39
AFP[a] (ng/dl)		12.97±24.07
INR[a]		1.1±0.12
S. Creatinine[a] (mg/dl)		0.93±0.25

[a]Data are expressed as Mean and standard of deviation (SD)

Comparative statistics

Comparison of different laboratory measurements showed a significant increase in serum creatinine over the 12-week treatment compared to baseline (0.9337) ($p < 0.01$). However, there was no significant change in WBC monitoring levels (p-value= 0.23); it increases non-significantly gradually over the 12 weeks of treatment compared to pre-treatment levels. However, mean hemoglobin levels show a minute decrease from baseline over the 12 weeks of therapy ($p < 0.01$). In addition, the average platelet count increased significantly over the 12 weeks of treatment ($p < 0.01$) (Table 3).

Table (3): Baseline and follow-up laboratory tests of the studied group (n = 102)

Variable	Pretreatment mean ± SD	W4 mean ± SD	W8 mean ± SD	W12 mean ± SD	P value
S. Creatinine[a] (mg/dl)	0.9337(0.248)	0.9728(0.210)	0.9915(0.187)	1.0254(0.186)	< 0.01
WBCs (×10 ^{3}mm^{3})	6.118(1.985)	6.626(2.169)	8.771(19.374)	6.847(2.358)	0.23
HB (g/dl)	13.831(1.454)	13.534(1.317)	13.464(1.399)	13.371(1.402)	< 0.01
PLT (×10 ^{3}/mm^{3})	172.95(55.71)	183.77(55.92)	185.97(63.108)	186.98(57.60)	< 0.01

Significant if P value <0.05 and highly significant if P value <0.001),[a] Data are expressed as Mean and standard of deviation (SD)

Virological response of studied patients

According to Table (4), assessment of the effectiveness of antiviral treatment reveals that 99 patients of 102 (97.1%) responded well for the treatment while only 3 cases were non-responders for the treatment.

Table (4): Virological response of studied patients

Time	(N)	(%)
Non-responders	3 of 102	2.9%
Responders	99 of 102	97.1%

Studying safety of antiviral treatment reveals that seventy-two (78.4%) had no side effects while twenty-two patients (21.5%) had mild side effects; most commonly headache (5.9%), fatigue (4.9%), diarrhea (2.9%). Nausea, asthenia, insomnia, thrombocytopenia each shows 1% while abdominal colic and vertigo each shows 2% as shown in (Table 5).

Table (5): Side effects in the studied patients

Side effects	No. (%) (n = 102)
No side effects	80 (78.4)
∗With side effects	22(21.5)
Headache	6(5.9)
Fatigue	5(4.9)
Diarrhea	3(2.9)
Nausea	1(1)
Asthenia	1(1)
Insomnia	1(1)
Thrombocytopenia	1(1)
Abdominal colic	2(2)
Vertigo	2(2)

Discussion

HCV is a blood borne disease that affects susceptible people, predominantly; in developing countries **(Jefferies *et al*., 2018; Obeagu *et al*., 2018).** The WHO has reported 290, 000 death cases from HCV alone due to either cirrhosis or HCC; worldwide **(WHO, 2022)**.

Although the global burden of HCV is estimated as 58 million infections **(WHO, 2022)**, in Egypt, HCV infection is one of the most predominant viral hepatitis **(Anwar *et al*., 2021)** representing about 4.5% to 6.7% of the total population in Egypt **(Doss, Hermez, Atta, & Jabbour, 2018)** . This suggests that more than 6 million people are infected with HCV in Egypt **(Cornberg *et al*., 2011)**.

WHO guidelines has pointed to the efficacy of DAAs as pangenotypic combination where they showed high efficacy against all 6 HCV genotypes **(Zoratti *et al*., 2020)**. Therefore, sofosbuvir combination therapy is recommended for SVR of 12 weeks or (SVR12). This lowers the rate of viral relapse. These regimens are permitted for managing HCV-infected patients without cirrhosis **(Zoratti *et al*., 2020)**. Giving a SVR12 for SOF/VEL of 95–100% in more than 1100 patients with HCV all six genotypes **(Cheng *et al*., 2021)**.

Accordingly, this study aimed to measure SVR12 of HCV patients treated within 12 weeks of sofo-velpa-voxilaprevir (Vosevi) in 102 adult chronic HCV patients who failed to respond to treatment by sofosbuvir plus daclatasvir combination regimen in Egypt.

In this study, evaluation of the effectiveness of antiviral therapy showed a sustained virological response rate of 97.1%, while only 3 of 102 patients remained unresponsive after 12 weeks of therapy. Our study results come from two randomized controlled trials that showed a higher percentage of patients treated with SOF/VEL/VOX who had failed previous treatment with DAA, showed SVR 12 **(CADTH, 2018)**. In POLARIS-1, 96.2% of SOF/VEL/VOX-treated patients without cirrhosis or with compensated cirrhosis, and with any genotype chronic HCV infection and previously treated with a DAA regimen containing an NS5A inhibitor, achieved an SVR of 12 **(Lawitz *et al*., 2017)**. In the POLARIS-4 study (N = 333), 97.8% of chronic HCV patients without cirrhosis or patients with genotype 1-4 HCV infection with compensated cirrhosis who were previously treated with an HCV regimen without an NS5A inhibitor achieved SVR 12 with SOF/VEL/VOX treatment for 12 weeks

(Bourlière *et al.*, 2017). Furthermore, in patients treated with SOF/VEL/VOX for 12 weeks, 74% of patients showed undetectable HCV at 4 weeks and 99% at 12 weeks. However, treatment failure included 6 relapses and 1 virological failure **(Degasperi *et al.*, 2019)**. Also, 98% SVR at 8 weeks **(Jacobson *et al.*, 2017)**. Similar results were obtained by the THASL Collaborative Group for the Study of the Use of Direct Acting Antivirals for chronic hepatitis C and **Wilson *et al.*, 2018; Charatcharoenwitthaya *et al.*, 2020; Wilson *et al.*, 2019**. In addition, another study revealed that SOF/VEL/VOX fixed-dose regimen has demonstrated highly effective therapy in both treatment-naïve and treatment-experienced patients. It achieved higher rates of virologic cure, in spite of previous use of DAAs for HCV treatment (including NS5A inhibitors) or the presence of RASs. **(Mathur *et al.*, 2019)**. In fact, one study has revealed that 94% of subjects achieved SVR 12 with re-treatment of VOSEVI after failed glecaprevir/pibrentasvir (G/P) (Mavyret) and were 90% harboring nonstructural 5A inhibitor resistance-associated mutations at baseline **(Pearlman *et al.*, 2019)**. A meta-analysis of 15 included studied about the safety and efficacy of SOF/VEL/VOX on HCV-chronic patients who failed previous treatment. SVR12 rates were 93% in the intention-to-treat populations (n=1517, 11 cohorts) and 96%. SVR12 rates were significantly higher in non-genotype 3 infected patients (OR = 2.29, P = 0.009) and non-cirrhotic patients (OR = 2.22, P = 0.03) than in genotype 3 and cirrhotic patients. In addition, SVR12 rates of previous SOF/VEL therapy were significantly lower than those of other regimens ($P \leq 0.001$) **(Xie *et al.*, 2022)**.

As regards to safety, studying safety of the antiviral treatment in our study revealed that 78.4% of the patients had no side effects while 21.5% had mild side effects; most commonly headache (5.9%), fatigue (4.9%), diarrhea (2.9%). Nausea, asthenia, insomnia, thrombocytopenia each showed 1% while abdominal colic and vertigo each showed 2%. Similar results were revealed by **(Degasperi *et al.*, 2019)** where cirrhosis ($p = 0.005$) and hepatocellular carcinoma ($p = 0.02$) were predictive factors for treatment failure. Adverse effects included fatigue (6%), hyperbilirubinemia (6%) and anemia (4%). Comparable side effects were retrieved by **(Jacobson *et al.*, 2017)** regarding treatment with sofosbuvir-velpatasvir-voxilaprevir as well as **(Llaneras *et al.*, 2019)** where most of the side effects were similar to ours. In the contrary, **Papaluca *et al.*, 2020**

revealed a serious side effect within small number of patients who were treated with SOF/VEL/VOX and had led to discontinuation during the first week in three participants. Two of these patients developed severe abdominal pain and one had a decrease in eGFR to 17 ml/min/m^2. Three cases of liver failure were observed during treatment. One of 18 patients with previous HCC had recurrence of HCC and one discontinued treatment within the first week due to abdominal pain, otherwise no other adverse events were observed in this group.

The study attributed these side effects to the already advanced liver cases of the patients **(Papaluca *et al.*, 2020)**. Furthermore, most adverse events detected by another study resulted from advanced liver disease or known toxicities of ribavirin. similarly, other studies have concluded the same mild adverse events following the administration of Sofosbuvir/ Velpatasvir/Voxilaprevir **(Bourlière *et al.*, 2017, 2018; Heo & Deeks, 2018; Solomon *et al.*, 2022)**. In the same line, **Feld *et al.*, 2015** have patients who were previously treated with PEG IFN-α /RBV and/or a protease inhibitor and the study revealed that Vosevi administration for 12 weeks showed a SVR of 99% among genotypes 1 to 6. Nevertheless, no adverse events among patients on sofosbuvir-velpatasvir were detected. Only two patients had virologic relapse. Besides, SOF/VEL/VOX showed no adverse events in HIV infected patients **(Da, Lourdusamy, Kushner, Dieterich, & Saberi, 2020)**.

Along the same lines, Gupta et al. showed that treatment with sofosbuvir (400 mg), velpatasvir (100 mg) and voxilaprevir (100 mg) for 12 weeks resulted in a total of 18% of 10 grade 3, 4 or 5 adverse events, including 8 hypertension and 3 all, of the following: cataract, diabetes, gastrointestinal bleeding, joint pain, lower back pain, vaginal cancer and sudden death. Four of these actions were classified as serious adverse events leading to hospitalization. One sudden death occurred at home of unknown cause four weeks after the end of treatment. No serious side effects were observed while using the drugs **(Gupta *et al.*, 2022)**.

Regarding laboratory measures, our study revealed significant increase in serum creatinine over the 12 weeks treatment in comparison with the baseline treatment (0.9337) ($p < 0.01$). No significant changes in the level of follow up of white blood cells (p value = 0.23) however; it was insignificantly increased gradually over the 12 weeks of treatment in comparison with pretreatment level. Nevertheless, mean hemoglobin levels showed minute

decrease over the 12 weeks of treatment in comparison with baseline levels ($p < 0.01$). Furthermore, mean platelets showed significant increase over the 12 weeks of treatment ($p < 0.01$). Although there is a scarce of data regarding the laboratory work changes during 12 weeks treatment with SOF/VEL treatment, one study has revealed that among 823 HCV infected patients, only 6 patients had an elevation of more than 3 folds in total serum bilirubin level, two patients had an elevation of more than 5 folds in serum AST and ALT level however, none of these adverse effects has led to discontinuation of SOF/VEL treatment **(Huang *et al.*, 2021)**. In the same line, bilirubin level was decreased (improved) in 17.9% of the patients after the administration of SOF/VEL combination therapy for 12 weeks (Annex I Summary Of Product Characteristics, 2022).

Similarly, SVR12 was achieved in patients receiving SOF/VEL combination therapy, but low mean platelet count, low mean albumin, and low mean bilirubin were all associated with 12-week treatment, inconsistent with our study results **(Gayam *et al.*, 2018)**. Overall, case reports documented that Sofosbuvir was associated with typical elevations in bilirubin and the onset of liver failure, including prolonged prothrombin time, decreased serum albumin, and ascites and hepatic encephalopathy **(Bethesda, 2012).** Unfortunately, our study could not detect such data in our sample due to lack of recorded data.

Recommendation & conclusion:

This study concluded that combination therapy (Velpatasvir-containing regimens) is effective in patients who have failed combination therapy with sofosbuvir plus daclatasvir, and safety is significant in HCV-treated patients in Egypt.

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فعالية وأمان العقار المحلي المحتوي علي مادة (فيلباتاسفير) لمرضي الالتهاب الكبدي المزمن بفيرس سي الغير مستجابين للعلاج بمادتي (السوفوسبوفير والدكلاتاسفير) في مصر

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التهاب الكبد الفيروسي هو مصدر قلق صحي عالمي يصيب ملايين الأشخاص كل عام. من بين الفيروسات المعروفة التي تصيب الكبد فيروسات التهاب الكبد A-E حيث يمكن أن يؤدي البعض إلى عواقب وخيمة وحتى الموت .

تهدف هذه الدراسة إلى دراسة فعالية وسلامة النظام العام (الذي يحتوي على الفيلباتسفير) بين ١٠٢ من مرضى التهاب الكبد الوبائي المزمن البالغين المصابين بفيروس التهاب الكبد الوبائي الرئوي في مصر.

هذه دراسة جماعية محتملة حيث تم تجنيد ١٠٢ مريضًا مزمنًا بفيروس التهاب الكبد الوبائي (HCV-RNA) الذين فشلوا في الاستجابة للعلاج من خلال العلاج المركب (sofosbuvir و daclatasvir). كشف تقييم فعالية العلاج المضاد للفيروسات عن استجابة مستدامة لعلم الفيروسات بنسبة ٩٧.١٪ بينما كان ٣ فقط من كل ١٠٢ مريض غير مستجيبين للعلاج بعد ١٢ أسبوعًا من العلاج.

فيما يتعلق بالسلامة، كشفت دراسة سلامة العلاج المضاد للفيروسات في دراستنا أن ٧٨.٤٪ من المرضى ليس لديهم آثار جانبية بينما ٢١.٥٪ لديهم آثار جانبية خفيفة ؛وهي في الغالب الصداع (٥.٩٪)، التعب (٤.٩٪)، الإسهال (٢.٩٪). أظهر كل من الغثيان والوهن والأرق وقلة الصفيحات ١٪ بينما أظهر كل من مغص البطن والدوار ٢٪.

كشفت دراستنا عن زيادة كبيرة في كرياتينين المصل على مدار ١٢ أسبوعًا من العلاج مقارنة بالعلاج الأساسي (٠.٩٣٣٧) (ص < ٠.٠١). ومع ذلك، لا توجد تغييرات كبيرة في مستوى متابعة خلايا الدم البيضاء (p value = 0.23) ؛ فقد زاد تدريجياً زيادة طفيفة على مدى ١٢ أسبوعاً من العلاج مقارنة بمستوى المعالجة المسبقة. ومع ذلك، أظهرت مستويات الهيموغلوبين المتوسطة انخفاضًا دقيقًا خلال ١٢ أسبوعًا من العلاج مقارنة بمستويات خط الأساس ($p < 0.01$). علاوة على ذلك، أظهر متوسط الصفائح الدموية زيادة كبيرة خلال ١٢ أسبوعًا من العلاج ($p < 0.01$).