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Comparison between Different Lines of Antiviral Combination Therapies against Hepatitis C Virus Genotype 4 in Egyptian Patients

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ABSTRACT

Background: hepatitis C virus (HCV) infection in one of worldwide chief causes chronic liver illness. The extended effect of it is highly inconstant, ranging from least histological changes to broad fibrosis and cirrhosis with possibility of hepatocellular carcinoma (HCC). The morbidity and mortality of this global infection are growing. The estimated worldwide prevalence of HCV is a by the World Health Organization (WHO) affecting >170 million people worldwide. There is a varied distribution of HCV infection with about 23 million people likely to have it in the countries of Eastern Mediterranean Region. This is nearly number of infected people in both Americas and Europe. Egypt is considered to have highest prevalence worldwide with an expected 14.7% of total population seropositive for HCV.

Aim of the Work: to compare the different new lines of antiviral combination therapies against hepatitis C virus genotype 4 in Egyptian patients as regards efficacy and safety.

Material and Methods: an open label, single-center, parallel-groups, randomized controlled clinical study, comparing the different lines of antiviral combination therapies against hepatitis C virus in Egyptian patients as regards efficacy reflected by the sustained virological response and safety through reporting adverse effects occur with each drug combination. This study was conducted on confirmed HCV chronically infected patients with diagnosis based on HCV-RNA PCR. The cases were collected from viral hepatitis treatment unit in Electricity hospital, one of the centers of National Committee for Control of Viral Hepatitis (NCCVH). All cases in this study were assessed and managed according to updated guidelines by NCCVH in parallel with the European Association for Study of Liver (EASL) and the American European Association for Study of Liver (AASLD).

Results: this study was conducted on 1000 patients with confirmed diagnosis of chronic HCV with positive serum HCV RNA by PCR technique. The cases were collected for this study had chronic hepatitis either without cirrhosis or with compensated cirrhosis differentiated by using the FIB-4 score. They could be INF-naïve or INF-experienced. The antiviral regimens used were SOF/SIM, SOF/LDV±RBV, SOF/DCV±RBV, PAR/OMB/RBV, and IFN/SOF/RBV. Out of 1737 patients who underwent initial evaluation, 531 patients were not eligible for therapy due to the presence of one or more exclusion criteria. The main causes for treatment exclusion were advanced liver decompensation, inadequately controlled diabetes and HBV co-infection. The total number of patients enrolled and eligible for antiviral treatment was 1206, 1000 of them started the treatment course, while 206 patients did not start it due to receiving treatment in other centres or died before starting the treatment.

Conclusion: 1000 patients started antiviral therapy for HCV, they showed good adherence to treatment and high SVR rates compared to other recently published real-life studies. We used seven different treatment regimens, all of which proved to be efficacious and safe with no clear preference for each over others.

Keywords: Antiviral Combination Therapies, Hepatitis C Virus Genotype 4

INTRODUCTION

Hepatitis C virus (HCV) infection in one of worldwide chief causes chronic liver illness. The extended effect of it is highly inconstant, ranging from least histological changes to broad fibrosis and cirrhosis with possibility of hepatocellular carcinoma (HCC). The morbidity and mortality of this global infection are growing [(1)]. The estimated worldwide prevalence of HCV is a by the World Health Organization (WHO) affecting >170 million people worldwide. There is a varied distribution of HCV infection with about 23 million people likely to have it in the countries of Eastern Mediterranean Region. This is nearly number of infected people in both Americas and Europe. Egypt is considered to have highest prevalence worldwide with an expected 14.7% of total population seropositive for HCV [(2)]. HCV has 6 most important genotypes (GTs) and the genetic multiplicity of HCV has been clearly related to the topographical spreading of it in different populations. HCV GT4 appears in about 8% of chronic HCV infections worldwide; it is predominant HCV genotype in Middle East & Africa, especially Egypt (90%) [(3)]. The main aim of hepatitis C treatment is to therapy the infection. An additional objective of it is to prevent their complications, as necro-inflammatory process, stiffness, cirrhosis with or without decompensation, HCC, serious extra-hepatic signs and death [(4)]. The definition of sustained virological response (SVR) is nonappearance of HCV RNA after treatment accomplishment. The infection is cured in more than ninety nine percent of patients who reach a SVR

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which is commonly accompanying with determination of hepatic illness in non-cirrhotic patients. Cirrhotic patients stay at risk of life-threatening complications; however liver stiffness may regress and the danger of complications such as hepatic failure and portal hypertension is decreased. Existing documents mention that HCC risk and all-cause mortality is significantly declined, but not eliminated, in cirrhotic patients who clear infection paralleled to non-treated and responded patients [(1)]. Until 2011, pegylated interferon (PEG IFNα) and ribavirin (RBV) combination for 24 to 48 weeks was the official HCV therapy which was achieved an intermediate SVR rates in GT4 patients [(5)]. Direct-acting antiviral (DAA) agents' discovery has significantly enhanced therapeutic outcomes for HCV patients. In 2011, GT 1 infection was allowed to be treated with telaprevir and boceprevir. Both medicines are first-wave, first generation DAAs and both target HCV NS3-4A serine protease and are thus referred to as protease inhibitors [(6)]. Three new HCV DAAs have been accredited in European Union in 2014, for use in HCV infection as combination therapies. Sofosbuvir, a nucleotide analogue that is pan genotypic HCV RNA inhibitor, a dependent RNA polymerase, has been approved in Jan 2014. Simeprevir, a 2nd wave, 1st generation NS3-4A protease inhibitor used with GT1 & 4 has been permitted in May 2014. Daclatasvir, a NS5A inhibitor, and pan genotypic DAA has been accepted in Aug 2014 [(7)]. Recently, several DAA-based regimens have been assessed in GT4 infection, including combinations of a DAA with traditional therapy (IFN/RBV) and more recently, interferon free regimens [(8)]. All treatment-naïve and -experienced HCV patients with compensated or decompensated cirrhosis should be measured for therapy. In 2015, six treatment choices are offered for GT4 infected patients treatment, including two IFN-containing regimens and four IFN-free regimens [(9)].

AIM OF THE WORK

To compare the different new lines of antiviral combination therapies against hepatitis C virus genotype 4 in Egyptian patients as regards efficacy and safety.

PATIENTS AND METHODS

An open label, single-center, parallel-groups, randomized controlled clinical study, comparing the different lines of antiviral combination therapies against hepatitis C virus in Egyptian patients as regards efficacy reflected by the sustained virological response and safety through reporting adverse effects occur with each drug combination. This study was conducted on confirmed HCV chronically infected patients with diagnosis based on HCV-RNA PCR. The cases were collected from viral hepatitis treatment unit in Electricity hospital, one of the centers of National Committee for Control of Viral Hepatitis (NCCVH). **The study was approved by the Ethics Board of Ain Shams University and an informed written consent was taken from each participant in the study.** The study was designed to include 1000 patients classified according to new HCV treatment regimens into five groups. Each group contains 200 patients divided into two main subgroups: INF-naïve and INF-experienced, each subgroup contains 100 patients. The sample size justification was done depending on **Doss *et al.*** [(10)] who found that SVR in SOF & RBV 77% and on **Mangia *et al.*** [(11)] who found that SVR in SOF, PegIFN and RBV 90% as well as on ***Alqahtani et al.*** [(12)] who found that SVR in SOF & LDV with or without RBV 97%. Assuming $\alpha = 0.05$ and power = 80% and by using PASS 11th release the minimal sample size for a clinical trial to study differences between regimens 84. In consideration to a possible 10% drop out of cases, so the enrolled cases was 100 cases in each group. ***Inclusion criteria:*** egyptian adult patient aged (18-75) years old, documented diagnosed HCV by positive RNA PCR, treatment-Naïve or INF-Experienced patients, patients with chronic hepatitis either Non-cirrhotic or Compensated cirrhotic (Child A), INF based group considerations: HB% ≥ 12 g/dl, TLC ≥ 4000/mm^3, PLT ≥ 150.000 /mm^3, INR ≤ 1.2. ***Exclusion criteria:*** other hepatitis causes viral or non-viral except HCV, patients with decompensated cirrhosis (Child B & C), CKD with eGFR ≤ 30 ml\min except after nephrological consultation (Enrolled in Group D), HCC, except 12 weeks after intervention aiming at cure with no evidence of activity by imaging, extra-hepatic malignancy except after 2 years of free interval and oncological consultation, inadequately controlled diabetes (HbA1c > 9%), pregnancy or inability to use effective contraception, INF based group considerations: presence of current auto-immune diseases, presence of current proliferative retinopathy, presence of unstable cardiac disease, presence of unstable neuropsychiatric disease. We

had followed the HCV treatment protocol of NCCVH in May 2015 and December 2016. Each patient had a designed treatment file that contains: application form, general status, laboratory results, treatment plan, and treatment follow ups in week 4,8,12, and 24. All patients included in this study were subjected to a baseline evaluation, monthly observation while treatment (Week-4 follow up & Week-8 follow up), end of treatment assessment and three months' post treatment follow up. The major five groups of patients: Group A: Sofosbuvir + Simeprevir ± Ribavirin :A fixed-dose combination of sofosbuvir (400 mg) and simeprevir (150 mg) once daily for 12 weeks. Group B: Sofosbuvir + Ledipasvir ± Ribavirin: A fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) once daily for 12 weeks. Group C: Sofosbuvir + Daclatasvir ± Ribavirin A fixed-dose combination of sofosbuvir (400 mg) and daclatasvir (60 mg) once daily for 12 weeks. Group D: Paritaprevir/Ombitasvir/ Ritonavir + Ribavirin: A fixed-dose combination of ombitasvir (12.5 mg), paritaprevir (75 mg) and ritonavir (50 mg) in one single tablet (two tablets once daily with food), and daily weight based ribavirin for 12 weeks. Group E: Sofosbuvir + PegIFN + Ribavirin: A fixed-dose combination of sofosbuvir (400 mg), weekly pegylated interferon & daily weight based ribavirin for 12 weeks. **Statistical analysis:** The collected data were verified, coded by the researcher and analyzed by using the IBM-Statistical Package for Social Sciences (IBM-SPSS 21). Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when their distribution found parametric. Also qualitative data were presented as number and percentages. The comparison between two independent groups with qualitative data was done by using Chi-square test and/or Fisher exact test only when expected count in any cell found less than 5. The comparison between two independent groups with quantitative data and parametric distribution was done by using Independent t-test. The comparison between more than two independent groups with quantitative data and parametric distribution was done by using One Way Analysis of Variance (ANOVA.(The comparison between more than two paired groups with quantitative data and parametric distribution was done by using Repeated Measures ANOVA. The confidence interval was set to 95% and the margin of error accepted was set to 5%.

RESULTS

Table (1): Treatment outcomes of all studied groups

Treatment regimens		Basal No.	Responder		Non-responder		Incomplete TTT	
			No	%	No	%	No	%
Group A (SIM/SOF)	**Naïve**	100	97	97.0	2	2.0	1	1.0
	Experienced	100	95	95.0	5	5.0	0	0.0
	Cirrhotic	59	55	93.2	4	6.8	0	0.0
	Non-cirrhotic	141	137	97.2	3	2.8	1	0.8
	without RBV	200	192	96.0	7	3.5	1	0.5
	Total	**200**	**192**	**96.0**	**7**	**3.5**	**1**	**0.5**
Group B (SOF/LDV ± RBV)	**Naïve**	100	97	97.0	3	3.0	0	0.0
	Experienced	100	98	98.0	1	1.0	1	1.0
	Cirrhotic	45	43	95.6	1	2.2	1	2.2
	Non-cirrhotic	155	152	98.1	3	1.9	0	0.0
	with RBV	169	165	97.6	3	1.8	1	0.6
	without RBV	31	30	96.8	1	3.2	0	0.0
	Total	**200**	**195**	**97.5**	**4**	**2.0**	**1**	**0.5**
Group C (SOF/DCV±RBV)	**Naïve**	100	98	98.0	1	1.0	1	1.0
	Experienced	100	96	96.0	3	3.0	1	1.0
	Cirrhotic	50	47	94.0	2	6.0	1	2.0
	Non-cirrhotic	150	147	98.0	2	2.0	1	0.6
	with RBV	109	105	96.3	3	2.8	1	0.9
	without RBV	91	89	97.8	1	1.1	1	1.1
	Total	**200**	**194**	**97.0**	**4**	**2.0**	**2**	**1.0**
Group D (PAR/OMB/RBV)	**Naïve**	100	97	97.0	3	3.0	0	0.0
	Experienced	100	96	96.0	4	4.0	0	0.0
	Cirrhotic	16	15	93.8	1	6.2	0	0.0
	Non-cirrhotic	184	178	96.7	6	3.3	0	0.0
	with RBV	200	193	96.5	7	3.5	0	0.0
	Total	**200**	**193**	**96.5**	**7**	**3.5**	**0**	**0.0**
Group E (SOF/INF/RBV)	**Naïve**	100	97	97.0	2	2.0	1	1.0
	Experienced	100	94	94.0	6	6.0	0	0.0
	Cirrhotic	4	4	100.0	0	0.0	0	0.0
	Non-cirrhotic	196	187	95.4	8	4.1	1	0.5
	with INF 2a	81	76	93.8	5	6.2	0	0.0
	with INF 2b	119	115	96.6	3	2.5	1	0.9
	Total	**200**	**191**	**95.5**	**8**	**4.0**	**1**	**0.5**
Total		1000	965	96.5	30	3.0	5	0.5

The treatment outcomes as regard response and non-response rates among studied groups was as following: the total sustained virological response (SVR) and non-SVR rates among treated patients were 96.5% and 3.1%, respectively; the SVR rates recorded with SIM/SOF, SOF/ LDV±RBV, SOF/DCV±RBV, PAR/OMB/RBV, and INF/SOF/RBV regimens were 96.0% , 97.5%, 97.0%, 96.5%, and 95.5%, respectively; the non-SVR rates recorded with SIM/SOF, SOF/ LDV±RBV, SOF/DCV±RBV, PAR/OMB/RBV,

and INF/SOF/RBV regimens were 3.5% , 2.5%, 2.0%, 3.5%, and 4.0%, respectively.

Table (2): Treatment outcomes in each group of all studied groups

	Group	A	B	C	D	E	P_{value}
Responders	Wk-4 response	152(76.0%)	148(74.0%)	158(79.0%)	163(81.5%)	143(71.5%)	0.138
	Wk-8 response	197(98.5%)	199(99.5%)	197(98.5%)	199(99.5%)	197(98.5%)	0.697
	ETR	196(98.0%)	197(98.5%)	196(98.0%)	197(98.5%)	195(97.5%)	0.945
	SVR	192(96.0%)	195(97.5%)	194(97.0%)	193(96.5%)	191(95.5%)	0.830
Non-responders	1ry non-responders	2(1.0%)	1(0.5%)	1(0.5%)	1(0.5%)	2(1.0%)	0.929
	Breakthrough	1(0.5%)	2(1.0%)	1(0.5%)	2(1.0%)	2(1.0%)	0.944
	Relapses	4(2.0%)	1(0.5%)	2(1.0%)	4(2.0%)	4(2.0%)	0.607
	Total non-responders	7(3.5%)	4(2.0%)	4(2.0%)	7(3.5%)	8(4.0%)	0.662
Un-TTT	Adverse effects	1(0.5%)	1(0.5%)	1(0.5%)	0(0.0%)	1(0.5%)	0.909
	Death	0(0.0%)	0(0.0%)	1(0.5%)	0(0.0%)	0(0.0%)	#1.000

Chi square test, #Fisher's Exact

The treatment outcomes as regard response rates (Week-4 response, Week-8 response, End of treatment response and Sustained virological response rate) and non-response rates (Non-response, 1ry non-response, Relapses and Breakthrough rate) among the studied groups was not significantly different.

Table (3): Comparison between SVR & Non-SVR patients regarding baseline characteristics

Predictors		SVR	Non-SVR	P_{value}
General	Age	53.5±9.4	53.7±8.2	0.908
	PCR	1.2±2.3	1.7±1.9	0.239
	Child	4.8±0.2	5.4±0.5	**<0.001***
	FIB-4	1.3±1.9	3.0±1.4	**<0.001***
Gender	Male	901(93.4%)	29(96.7%)	0.471
	Female	64(6.6%)	1(3.3%)	
Special Habits	Smoker	228(23.6%)	8(26.7%)	0.699
	Non Smoker	737(76.4%)	22(73.3%)	
Chronic illness	HTN	160(16.6%)	4(13.3%)	0.636
	DM	307(31.8%)	9(30.0%)	0.833
Child	A5	853(88.4%)	17(56.7%)	**<0.001***
	A6	112(11.6%)	13(43.3%)	
Fibrosis Stage	Cirrhotic	163(16.9%)	9(30.0%)	0.061
	Non-cirrhotic	802(83.1%)	21(70.0%)	
Patient Type	Naïve	486(50.4%)	11(36.7%)	0.139
	Experienced	479(49.6%)	19(63.3%)	
Laboratory Investigations	ALT	53.8±5.2	60.6±6.0	0.415
	AST	45.5±4.8	52.5±9.6	0.349
	Bilirubin	0.6±0.03	1.15±0.05	**<0.001***
	Hemoglobin	14.7±1.5	14.7±1.3	1.000
	WBCs	7.3±1.1	6.1±1.5	**0.035***
	Platelets	245.5±69.8	144±54	**<0.001***
	Albumin	4.3±0.4	3.9±0.3	**<0.001***
	INR	1.09±0.19	1.11±0.1	0.566
	Creatinine	0.94±0.05	0.93±0.12	0.903
	AFP	2.8±0.8	17.9±6.6	**<0.001***

The Baseline Parameters was significantly different between SVR & Non-SVR patients. Albumin, leukocyte, and platelet count were significantly higher in SVR patient while AFP, bilirubin, FIB-4; and Child score were significantly higher in non-SVR patient. Age, gender, smoking status, presence of co-morbidities, PCR, transaminases, hemoglobin, INR, and creatinine level were insignificantly different between SVR & Non-SVR patients.

Table (4): Side effects occurrence among the studied groups

Side effects	Total	A	B	C	D	E	P_{value}
Headache	120 (12.0%)	26 (18.0%)	21 (15.5%)	24 (17.0%)	28 (19.0%)	21 (15.5%)	0.773
Fatigue	150 (15.0%)	31 (31.0%)	25 (17.5%)	20 (15.0%)	26 (18.0%)	48 (29.0%)	**<0.001***
Asthenia	69 (6.9 %)	11 (5.5%)	16 (8.0%)	12 (6.0%)	13 (6.5%)	17 (8.5%)	0.720
Insomnia	54 (5.4%)	9 (4.5%)	7 (3.5%)	5 (2.5%)	11 (5.5%)	22 (11.0%)	**0.002***
Dizziness	10 (1.0%)	1 (0.5%)	2 (1.0%)	1 (0.5%)	1 (0.5%)	5 (2.5%)	0.195
Irritability	20 (2.0%)	2 (1.0%)	3 (1.5%)	2 (1.0%)	0 (0.0%)	13 (6.5%)	**<0.001***
Depression	15 (1.5%)	0 (0.0%)	1 (0.5%)	3 (1.5%)	2 (1.0%)	9 (4.5%)	**0.002***
Nausea & Vomiting	77 (7.7%)	16 (8.0%)	12 (6.0%)	12 (6.0%)	13 (6.5%)	24 (12.0%)	0.123
Abdominal pain	29 (2.9%)	3 (1.5%)	5 (2.5%)	2 (1.0%)	3 (1.5%)	16 (8.0%)	**<0.001***
Diarrhea	53 (5.3%)	18 (9.0%)	13 (6.5%)	14 (7.0%)	16 (8.0%)	26 (13.0%)	0.150
Anorexia	64 (6.4%)	9 (4.5%)	8 (4.0%)	11 (5.5%)	5 (2.5%)	30 (15.0%)	**<0.001***
Wt. loss	24 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	24 (12.0%)	**<0.001***
Rash	43 (4.3%)	5 (2.5%)	6 (3.0%)	7 (3.5%)	5 (2.5%)	20 (10.0%)	**<0.001***
Pruritus	75 (7.5%)	15 (7.5%)	11 (8.0%)	9 (4.5%)	13 (6.0%)	27 (13.5%)	**0.006***
Flu-like	54 (5.4%)	5 (2.5%)	6 (3.0%)	4 (2.0%)	5 (2.5%)	34 (17.0%)	**<0.001***
Pyrexia	31 (3.1%)	5 (4.5%)	6 (3.0%)	6 (3.0%)	4 (2.0%)	26 (13.0%)	**<0.001***
Dyspnea	15 (1.5%)	2 (1.0%)	3 (1.5%)	0 (0.0%)	1 (0.5%)	9 (4.5%)	**0.002***
Cough	4 (0.4%)	0 (0.0%)	4 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**0.003***
Alopecia	36 (3.6 %)	1 (0.5%)	1 (0.5%)	2 (1.0%)	1 (0.5%)	31 (15.5%)	**<0.001***
Arthralgia	59 (5.9%)	10 (5.0%)	7 (3.5%)	8 (4.0%)	9 (4.5%)	25 (12.5%)	**<0.001***
Myalgia	85 (8.5%)	15 (7.5%)	10 (5.0%)	15 (7.5%)	16 (8.0%)	29 (19.5%)	0.011
Hyperbilirubinemia	131 (13.1%)	36 (18.0%)	24 (12.0%)	23 (11.5%)	35 (17.5%)	13 (6.5%)	**0.003***
Renal impairment	29 (2.9%)	5 (2.5%)	10 (5.0%)	1 (0.5%)	8 (4.0%)	5 (2.5%)	0.081
Anemia	121 (12.1%)	11 (5.5%)	22 (11.0%)	13 (6.5%)	25 (12.5%)	50 (25.0%)	**<0.001***
Hypersensitivity	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0.405
Decompensation	3 (0.3%)	1 (0.5)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0.735

$P_{(Groups)}$: Comparison between groups, ^Chi square test, #Fisher's Exact, *Significant

There was a significant difference as regard the frequency of side effects occurrence in different

treated groups. Fatigue, Insomnia, Depression, Irritability, Anorexia, Abdominal pain, Cough, Wt. loss, Rash, Pruritus, Flu-like, Pyrexia, Dyspnea, Alopecia, and Arthralgia was occurred primarily with Group E; Hyperbilirubinemia was prominent with Group A & D; Anemia was predominant with Group D & E; Renal impairment major with Group B & D; and. There were no significant differences as regard the frequency of side effects occurrence in different treated groups Headache, Asthenia, Dizziness, Nausea, Diarrhea, Myalgia, Hypersensitivity and Hepatic decompensation.

DISCUSSION

So much has been written and rewritten on hepatitis C virus, their properties, their morbidities, and their possible treatment options concerning their efficiency and risks. Directly acting antivirals (DAAs) are a new era in treating HCV and considered the key of its treatment. Since the introduction of DAAs in 2014, a huge effort has been made to control HCV in Egypt by implementing a national mass treatment program. As Egypt has the highest HCV worldwide prevalence rate, a unique mass treatment program was established. However, all patients in our study were treated with brand products at the governmental expenses entirely. The sequential availability of different DAAs in Egypt since 2014 has led to a series of changes in the Egyptian protocol for HCV treatment. In the current study, we present the real life experience of a single specialized center for HCV treatment in Egypt that involved seven different regimens. We aimed to compare the different available lines of antiviral combination therapies against HCV genotype 4 in Egyptian patients regarding efficacy and safety. The total number of referred patients to the center reached 1737 patient during the research period. After applying the inclusion and exclusion criteria for treatment, a total of 1000 patients started therapy, with only 5 patients lost during follow-ups, leaving a total of 995 patients who completed treatment & follow-up period. The study was performed in two stages: **Stage (1):** Started in May 2015 to May 2016 according to NCCVH protocol released in May 2015. In this stage patients classified into INF eligible patients treated with INF/SOF/RBV regimen and INF ineligible patients treated with SIM/SOF regimen. **Stage (2):** Started in Dec 2016 to Dec 2017 according to NCCVH protocol released in December 2016. In this stage patients classified into Easy to treat group treated with SOF/DCV, SOF/LDV or PAR/OMB/RBV regimens and Difficult to treat group treated with SOF/DCV/RBV, SOF/LDV/RBV or PAR/OMB RBV regimens. As regard **treatment responses** in the current study, the total sustained virological response (SVR) and non-SVR rates among treated patients were 96.5% and 3.1%, respectively; and according to the used regimens, the highest SVR rates were achieved with SOF/LDV±RBV, which was reached 97.5%. Similarly, SOF/DCV±RBV showed SVR rates of 97%; followed by PAR/OMB/RBV showed SVR rates of 96.5% then SIM/SOF and INF-based triple regimen, which had been used earlier in the project. The SVR rate of SIM/SOF was 96% and 95.5% for INF/SOF/RBV which had the lowest SVR rate. The non-SVR rates recorded with SIM/SOF, SOF/LDV±RBV, SOF/DCV±RBV, PAR/OMB/ RBV, and INF/SOF/RBV regimens were 3.5%, 2.5%, 2.0%, 3.5%, and 4.0%, respectively. Comparable rates were observed in most of published HCV treatment studies coming from real-life settings in Egypt as ***Elsharkawy et al.*** [13] and ***El Kassas et al***. [14]. Our results were nearly the same as those of another recent Egyptian studies as ***Eletreby et al.*** [15]**,** which evaluated naïve and experienced patients who received same treatment regimens. In this study, naïve patients treated with SIM/SOF, SOF/LDV±RBV, SOF/DCV±RBV, PAR/OMB/ RBV, and INF/SOF/RBV regimens showed SVR values of 97%, 97%, 98%, 97% & 97%, respectively; while experienced (INF previously treated) patients treated with same regimens showed a SVR values of 95%, 98%, 96%, 96% and 94%, respectively. Generally, naïve cases had *higher* treatment response rates than experienced in all treatment regimens except with LDV regimen which showed the highest response rate with experienced patients. Studied patients were classified into cirrhotic patients or non-cirrhotic patients according to FIB-4 score and abdominal ultrasound examination. The non-cirrhotic patients had higher treatment response rates than cirrhotic patients except with IFN regimen which related to the very small cirrhotic subgroup in this treatment group. On analyzing the baseline parameters of patients who failed to treatment, it was clear that those patients had *significantly lower* albumin, total leukocyte, & platelet count; or *higher* AFP,

bilirubin, FIB-4 and Child score; this is in same similarity with recent Egyptian studies ***Elbaz et al.*** [16]; ***Elsharkawy et al.*** [13]**,** in which predictors of non-response detected includes previous INF therapy, and being in the difficult-to-treat group. On the other hand, we found that age , gender, smoking status, presence of co-morbidities, PCR, transaminases, hemoglobin, and creatinine level were *insignificantly different* between patients with SVR and Non-SVR. Liver function parameters, serum albumin, bilirubin, platelet count, and international normalized ratio were improved *significantly* in the majority of studied patients; and that was featured in the **Child-Turcotte-Pugh score** values as 82 patients showed an improved Child score, while only 11 showed deterioration and that's concordant with ***Mohamed et al.*** [17]. The Child-Turcotte-Pugh score was *significantly* improved with LDV regimen in cirrhotic patients. Only in SIM regimen, *a significant declining* detected as regard compering Child score values before and after the treatment among the studied groups. Although progression in patients with chronic liver disease may be predicted, progression to Child–Pugh score B after completing treatment occurred with SIM, LDV & DCV regimens; it was highest in SIM regimen. Only in SIM regimen the development of Child–Pugh score B was *significantly higher* in cirrhotic than non-cirrhotic cases while *no significant difference* between cirrhotic and non-cirrhotic subgroups with other regimens. As reported in ***Fouad et al.*** [18] study, the **Fibrosis-4 score** was *significantly higher* in cirrhotic than non-cirrhotic patients in all groups before & after treatment. All studied groups showed *significantly declining* in FIB-4 score after completing treatment except with INF group. This could explained by significant improvement in parameters of liver fibrosis as PLT, ALT & AST levels after completing treatment regimens, which was reflected on FIB-4 as a *significant declination* in its values with patients achieved SVR. ***Hafez*** [19] said that the co-administration of direct antiviral agents of different classes increases the probability of side effects. In current study, we recorded **adverse effects** in 274 (27.4%) of treated patients with mean age (54 ± 9), male gender (73%). Most of side effects were mild in severity, the commonest side effects *Fatigue* (15%), *Hyperbilirubinemia* (13.1%), *Anemia* (12.1%), *Headache* (12%); and the least recorded side effects was *Dizziness* (1%), *Cough* (0.4%), *Hepatic decompensation* (0.3%), & *Hypersensitivity* (0.1%). INF/SOF/RBV showed the highest incidence in side effects occurrence among treated patients. Side effects were developed in 92 patients (46%) with this treatment regimen and was *significantly higher* than other regimes with Fatigue, Insomnia, Depression, Irritability, Anorexia, Abdominal pain, Weight loss, Flu-like, Pyrexia, Dyspnea, Cough, Alopecia, Arthralgia, Rash and Pruritus. As ***Attia et al.*** [20], this study showed that SOF/DCV±RBV had the lowest incidence in side effects occurrence among treated patients. Headache, Anorexia, Alopecia, Pruritus, Myalgia, and Anemia were *significantly higher* in ribavirin containing regimens with; while Nausea, Vomiting, and Diarrhea were *significantly higher* in ribavirin free regimens. Also, The frequency of occurrence of Headache, Fatigue, Depression, Nausea, Diarrhea, Anorexia, Pruritus, Pyrexia, Alopecia, Arthralgia, Myalgia, Anemia, Hyper-bilirubinemia and Hepatic decompensation were *significantly higher* in cirrhotic patients.Most common adverse effects were 'flu'-like symptoms as fatigue, myalgia, & fever, which didn't need management or were simply treated and didn't lead to treatment discontinuation. **Serious adverse events** (SAEs) were detected in this study as well as resemble studies like ***Elbaz et al.*** [16] In current study, among 1000 patients who were treated, five cases (0.5%) reported SAEs and prematurely stopped their treatment. *Hepatic decompensation* (three patients -one with each- SIM/SOF, SOF/LDV/RBV & SOF/DCV/RBV, patient in DCV group died in 1st month of treatment), *Hypersensitivity* (1 patient with SOF/DCV), and *Anemia* (1 patient with INF/SOF/RBV). HCC development was recorded in five cases (four patients with SOF/LDV/RBV and one patient with SOF/DCV/RBV, all were cirrhotic) during the post treatment follow-up by ultrasound examination which revealed hepatic focal lesion associated with significant AFP level elevation with mean of (456±393) and which was confirmed by tri-phasic CT abdomen. This findings may suggest a relation between HCC occurrences following SVR with IFN-free therapy but it could be related to baseline risk factors/patient selection. The Impact of different sofosbuvir based treatment regimens on the **biochemical profile** of chronic hepatitis C patients discussed by ***Negm et al.*** [21] and concluded that

DAAs improve liver necro-inflammatory markers in cirrhotic and non-cirrhotic. In this study, regarding the liver enzymes indices; both **Alanine & Aspartate amino-transaminase level** *significantly declined* during & after completion of treatment among all studied groups. The decline was remarkable early after starting treatment followed by nearly stabilization in ALT level in rest of treatment period except with INF group where the decline was gradual throughout the period of treatment. On the other hand, the **Total bilirubin level** was *significantly declines* after complete treatment periods among all studied groups, the declination was gradual at period of the treatment with transiently elevation in week 4 among the studied groups and prominent in 2D & SIM regimens. In contrast to what's ***Negm et al.*** [21] reported regarding the liver function indices; we recorded that the **serum Albumin level** was *significantly increased* in all studied groups, but only in INF & DCV elevation proceeded by a slight transient declining the period of treatment then elevation take place; the transient declination is most in INF regimen with mean (4.1±0.3) and in DCV regimen with mean (4.0±0.5); while the **International normalized ratio** showed trivial changes in different follow up times among the studied groups. In other laboratory investigations some interesting findings need to be spotted as in **AFP level**, there was *significant declination* after ending treatment only with PAR/OMB/RBV regimen. As well, a *significant elevation* detected only in SIM/SOF regimen as regard **s. Cr levels**. Additional studies interested in those parameters required.

CONCLUSION

In the era of DAAs and with the rapidly growing experience with their use worldwide, especially in Egypt, this single-center account adds to the real-life experience in the treatment of chronic HCV. 1000 patients with chronic hepatitis C virus infection started direct acting antiviral therapy. They showed good adherence to treatment and high SVR rates compared to other recently published real-life studies. We used seven different treatment regimens, all of which proved to be efficacious and safe with no clear preference for each over others. Finally, we could say that with using DAAs, chronic hepatitis C disease outcomes became promising. The overwhelming majority of patients passed to SVR with minimal side effect but the correlation between the treatment and some adverse events still completely unclear.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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