The Egyptian Journal of Hospital Medicine (April 2018) Vol. 71 (7), Page 3591-3600

Comparative Study between Different Modalities of Treatment of HCV in New Era of Direct Acting Antiviral Drugs (DAAs) in Aswan Governorate

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ABSTRACT

Background: Hepatitis C virus (HCV) infection is considered a national progressing problem that threatens the life of Egyptian people as Egypt has the highest prevalence of HCV infection in the world with prevalence rates of 14.7 % of the adult population. HCV infection causes chronic hepatic inflammation and severe liver diseases, such as liver cirrhosis and hepatocellular carcinoma. Currently, HCV is curable, unlike HIV and HBV. Goals of therapy are to eradicate HCV infection to prevent hepatic cirrhosis, decompensation of cirrhosis, hepatocellular carcinoma (HCC) and death. End point of therapy: undetectable HCV RNA in a sensitive assay (<15 Iu /ml) 12 weeks sustained virological response (SVR12) and 24 weeks (SVR24) after the end of treatment.

Aim of the Work: To assess the efficacy of DAAs in the treatment of HCV in Aswan Governorate; and to compare between the different combinations of DAAs ± ribavirin ±interferon which were available during the study period as regards efficacy and possible side effects in each treatment combination.

Patients and Methods: This retrospective study was conducted in Aswan Fever Hospital, Aswan Hospital Health Insurance and Tropical Medicine Department Ain Shams University. Study population: Patients with chronic hepatitis C who received treatment in the period from January 2015 to July 2016. Group I: Triple therapy (Sofosbuvir + Ribavirin + Interferon) for 3 months. Group II: Sofosbuvir + Ribavirin for 6 months. Group III: Sofosbuvir + Simeprevir for 3 months. Group IV: Sofosbuvir + daclatasvir ± Ribavirin for 3 months.

Results: In Group I SVR was 74.3% ,Group II SVR was 60% ,Group III SVR was 85.7% and Group IV SVR was 100% **Conclusion:** This is a large real-life report of the use of very low-cost generic medications for treating HCV-G4 within the largest treatment programme worldwide. The use of entirely generic SOF DCV combination with or without generic RBV was well tolerated and associated with high response rate in patients with different stages of liver disease. This can be an example for other countries of similar limited resources for managing their patients with HCV.

Keywords: HCV, direct acting antiviral drugs.

INTRODUCTION

Hepatitis C is a disease with a significant global impact. According to the World Health Organization, there are about 150 million people chronically infected with the hepatitis C virus (HCV) corresponding to 2-2.5% of the world's total population [(1)].

Chronic hepatitis C is the most common cause of chronic liver disease and cirrhosis and the most common indication for liver transplantation in the United States (U.S), Australia, and most of Europe [(2)]. It is the most common chronic blood borne disease [(3)] and it is a progressive disease, the rate of progression is highly variable. HCV seroprevalence in Egypt 2008 was estimated to be 14.7%. Accordingly, Egypt has the highest HCV prevalence in the world caused by extensive iatrogenic transmission during the era of parenteral antischistosomal therapy mass campaigns [(4)]. Currently, HCV is curable, unlike HIV and HBV [(5)].

The goal of therapy is to cure HCV infection in order to prevent the complications of HCV-related liver and extrahepatic diseases, including hepatic necroinflammation, fibrosis, cirrhosis, decompensation of cirrhosis, HCC, severe extrahepatic manifestations and death. The endpoint of therapy is an SVR, defined by undetectable HCV RNA in blood 12 weeks (SVR12) or 24 weeks (SVR24) after the end of therapy, as assessed by a sensitive molecular method with a lower limit of detection 615 IU/ml [(6)].

AIM OF THE WORK

To assess the efficacy of DAAs in the treatment of HCV in Aswan Governorate; and to compare between the different combinations of DAAs ± ribavirin ±interferon which were available during the study period as regards efficacy and possible side effects in each treatment combination.

PATIENTS AND METHODS

Study design: Retrospective study.

Study setting: This study was conducted in Aswan Fever Hospital, Aswan Hospital Health Insurance and Tropical Medicine Department Ain Shams University.

Study population: Patients with chronic hepatitis C who received treatment in the period from January 2015 to July 2016. Total patients included in our study were 140 patients subdivided into four groups ,each group 35 patients.

- **Group I (35 patients):** Triple therapy (Sofosbuvir + Ribavirin + Interferon) for 3 months.
- **Group II (35 patients):** Sofosbuvir + Ribavirin for 6 months

Received:20 /3 /2018 DOI: 10.12816/0047680

Accepted:30 /3 /2018

- **Group III (35 patients):** Sofosbuvir + Simeprevir for 3 months
- **Group IV (35 patients):** Sofosbuvir + daclatasvir ± Ribavirin for 3 months.

All patients were subdivided into naive or experienced SVR or relapsed.

Evaluation tests for recruitment [(7)]:

CBC, AST, ALT, serum bilirubin (Total and direct), serum albumin, INR, HBsAg, AFP, ECG for patients above 50 Y, quantitative PCR assay for HCV RNA, abdominal ultrasonography, and pregnancy test for ladies in the childbearing period. If the patient was likely to receive IFN, the following tests were done: ANA, TSH, and fundus examination.

Inclusion Criteria [(7)]:

1. Age: 18 – 75 years.
2. HCV RNA positive.
3. Any BMI.
4. Treatment naive or treatment experienced.
5. All fibrosis stages.

Exclusion criteria [(7)]:

1. Total serum bilirubin > 3 mg.
2. Serum albumin < 2.8 g/dl
3. INR ≥ 1.7.
4. Platelet count < 50, 000/mm^3.
5. Ascites or history of ascites.
6. Hepatic encephalopathy or history of hepatic encephalopathy.
7. HCC, except 4 weeks after intervention aiming at cure with no evidence of activity by dynamic imaging (CT or MRI).
8. Serum creatinine > 2.5 mg/dl. If creatinine is between 1.5 and 2.5 mg/dl, eGFR should be calculated and should exceed 30 ml/min with favorable nephrological consultation.
9. Extrahepatic malignancy except after two years of disease-free interval.
10. Pregnancy or inability to use effective contraception.

Criteria for IFN eligibility included; Age: 18-60 years old, total bilirubin ≤ 1.2 mg/dl, serum albumin ≥ 3.5 g/dl. , INR ≤ 1.2. , hemoglobin ≥13 g/dl for males and ≥12 g/dl for females, TLC ≥ 4000/mm^3, absolute neutrophilic count ANC ≥ 1500/mm^3, platelet count ≥ 150.000/mm^3, ANA ≤ 2 folds, absence of current autoimmune diseases, including thyroid disease, adequately controlled diabetes mellitus (HbA1C ≤ 8%), absence of proliferative retinopathy, absence of unstable cardiac disease, non-organ transplant cases, absence of unstable neuro-psychiatric disorders, history of Peg IFN-documented intolerability, absence of esophageal and / or gastric varices.

METHODS

Medical records of patients with chronic HCV who received antiviral therapy for HCV in the period from January 2015 to July 2016 were retrospectively reviewed and their clinical characteristics and laboratory examination results were retrieved. Special emphasis on general condition, any newly developed complaints (e.g. fatigue, headache anemic manifestations, skin manifestations, ….), laboratory data including Liver function tests, complete blood picture and HCV PCR as shown in tables 1 to 4 according to National Committee for the Control of Viral Hepatitis (**NCCVH**) [(7)].

Baseline laboratory tests including a PCR test for viral load were accepted from external labs if performed during the preceding 3 months. All patients were entitled to free baseline, on-treatment, and post-treatment hematological, biochemical and viral load tests on the expense of the Ministry of Health (MoH). However, tests performed elsewhere in private labs during and after treatment were accepted and not repeated.

Statistical analysis was performed using appropriate statistical programs.

Statistical methods :

Analysis of data was done using SPSS program version18.Quantitative data were presented as mean and SD . Qualitative data were presented as count and percent.Independent samples t test was used to compare parametric quantitative data between two groups and Mann Whitney U test was used for non parametric quantitative data.One Way ANOVA test was used to compare quantitative data between more than two groups .Chi square test was used to compare qualitative data between different groups.P value < 0.05 was considered statistically significant.

RESULTS

Descriptive and Demographic data of the studied patients (n = 35 × 4)

Table (1): Comparison between the four groups regarding demographic data of patients:

		Group I N=35		Group II N=35		Group III N=35		Group IV N=35		F*	P value
		Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Age		51.37#	8.10	57.23#	7.72	56.60	8.38	53.29	10.84	3.10	**0.03**
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**X^{2**}**	**P value**
Sex	**male**	21	60.0	23	65.7	24	68.6	16	45.7	4.53	0.21
	female	14	40.0	12	34.3	11	31.4	19	54.3		

*One Way ANOVA test #post hoc test **Chi square test

Table 1: There was significant statistical difference between the four groups regarding the demographic data (Age), the oldest patient was 75 years and the youngest was 22 years.

Table (2): Initial evaluation before treatment for the different groups

		Group I		Group II		Group III		Group IV	
		N	%	N	%	N	%	N	%
Treatment status	Naïve	26	74.3	24	68.6	34	97.1	33	94.3
	Experienced (INF-based, SOV-based)	9	25.7	11	31.4	1	2.9	2	5.7
chronic diseases	No	22	62.9	18	51.4	19	54.3	22	62.9
	DM	8	22.9	7	20.0	1	2.9	3	8.6
	HTN	3	8.6	4	11.4	5	14.3	5	14.3
	DM and HTN	2	5.7	6	17.1	10	28.6	5	14.3
Abdominal U/S	non cirrhotic	24	68.6	16	45.7	19	54.3	24	68.6
	Cirrhotic	11	31.4	19	54.3	16	45.7	11	31.4

This table shows the difference between the four groups (initial evaluation) including treatment status, presence of chronic disease and abdominal ultrasound examination.

Group I: Patients on triple therapy (Sofosbuvir + Ribavirin + Interferon) for 3 months (n=35).

Table (3): Response to treatment and side effects of group I

		N	%
Response to treatment	**Cured**	26	74.3
	Relapse	9	25.7
side effects	**Anemia**	14	40
	Hyperbilirubinemia	6	17.2
	Anemia and hyperbilirubinemia	7	20
	NO	8	22.8

Table 3: 26 patients achieved SVR12 (74.3%).

There were 27 cases out of 35 cases showing side effects, the main side effects were anemia 14 cases (40 %), hyperbilirubinemia 6 cases (17.2%) and both anemia and hyperbilirubinemia in 7 cases (20%).

Group II: Patients on Sofosbuvir +Ribavirin for 6 months (n=35)

Table (4): The response to treatment and side effects among patients in group II

		N	%
Response to treatment	**Cured**	21	60.0
	Relapse	14	40.0
	Total	35	100.0
Side effects	**Anemia**	8	22.9
	Hyper bilirubinemia	19	54.3
	photosensitivity	3	8.6
	NO	5	14.2

Table 4: 21 cases (60%) achieved SVR12 and 14 patients (40%) were relapsers.

There were 30 cases out of 35 cases showing side effects, the main side effects were anemia 8 cases (22.9 %), hyper bilirubinemia 19 cases (54.3%) and photosensitivity in 3 cases (8.6%).

Group III: Patients on Sofosbuvir + Simeprevir for 3 months (n=35)

Table (5): The response to treatment and side effects among patients in group III

		N	%
Response to treatment	**Cured**	30	85.7
	Relapse	3	8.6
	Died	2	5.7
	Anemia	1	2.85
	Hyperbilirubinemia	9	25.7
	Photosensitivity	2	5.7
	anemia and hyperbilirubinemia	2	5.7
	Hepatic decompensation (ascitis and encephalopathy)	3	8.6
	hyperbilirubinemia and photosensitivity	1	2.85
	No	17	48.6

Table 5: 85.7% of cases achieved SVR. There were 18 cases out of 35 cases showing side effects, the main side effects were anemia (2.85 %), hyper bilirubinemia (25.7%), both anemia and hyperbilirubinemia (5.7%), photosensitivity (5.7%), ascites and encephalopathy (8.6%) and, both hyperbilirubinemia and photosensitivity (5.7%).

Group IV: Patients on Sofosbuvir + daclatasvir ± Ribavirin for 3 months (n=35).

Table (6): The response to treatment and side effects for group IV

		N	%
Response to treatment	**Cured**	35	100.0
Side effects	**Anemia**	5	14.3
	Hyperbilirubinemia	2	5.7
	Photosensitivity	2	5.7
	NO	26	74.3

Table 6: All patients achieved SVR. There were 18 cases out of 35 cases showing side effects, the main side effects were anemia (14.3%), hyper bilirubinemia (5.7%) and photosensitivity (5.7%).

Table (7): Comparison between patients of the four groups regarding laboratory tests before treatment**.**

	Group I		**Group II**		**Group III**		**Group IV**		**F***	**P – value**
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**		
HCV PCR	3179361.7	437197.3	1653805.6	376879.3	1581048.9	304359.9	2159438.2	332949.5	1.42	0.24
AST	39.68	6.25	46.33	8.51	49.86	7.95	41.83	7.81	1.29	0.28
ALT[#]	38.00	5.81	44.39	10.27	55.62	8.60	43.47	8.52	2.64	**0.052**
Total bilirubin [##]	.81	.13	.98	.14	.99	.20	.77	.11	4.40	**0.01**
Direct bilirubin	.34	.02	.49	.01	.43	.06	.32	.07	1.09	0.36
Albumin[###]	4.13	.72	3.77	.74	3.46	.48	4.11	.45	9.20	**<0.001**
INR	1.14	.12	1.16	.17	1.15	.13	1.51	.21	0.87	0.46
Hb	14.16	1.66	13.37	1.87	13.47	1.59	13.29	1.88	1.79	0.15
WBC	6.33	1.10	35.66	8.13	5.48	1.11	6.61	1.13	1.02	0.39
ANC	2.99	0.32	2.91	0.59	2.88	0.15	3.20	0.06	0.39	0.76
PLT	200.51	43.23	135.88	31.68	144.54	34.24	193.86	38.06	11.16	**<0.001**
RBS	102.26	14.37	109.88	23.34	127.77	26.43	99.96	16.01	2.31	0.08
HbA1c	7.64	.72	7.74	1.88	7.56	1.16	6.57	1.27	0.33	0.80
Creat.	.87	.17	.91	.11	.91	.13	.87	.16	0.45	0.72
AFP	10.76	16.78	9.94	9.71	8.07	7.40	9.87	15.43	0.24	0.87

*One Way ANOVA test

#post hoc test (group I vs group III)

##post hoc test (group II vs group IV) (group III vs group IV)

###post hoc test (group I vs group III) (group III vs group IV)

####post hoc test (group I vs group II) (group I vs group III) (group II vs group IV) (group III vs group IV).

Table 7 : There were statistically significant differences between the four groups regarding T. bilirubin, Albumin, Platelet count while there were no statistical differences between the four groups regarding the other lab results.

Table (8): Comparison between the different regimens regarding laboratory tests at 12 weeks.

	Group I		Group II		Group III		Group IV		F*	P value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
AST	30.71	6.03	34.09	7.27	33.80	7.70	26.87	6.13	0.79	0.50
ALT	28.42	5.99	27.87	4.15	29.24	6.47	27.38	5.81	0.08	0.97
Total bilirubin#	.86	.11	1.11	.18	1.33	0.25	.82	.16	3.68	**0.02**
Direct bilirubin	.24	.02	.50	.05	.55	.11	.29	.05	0.87	0.47
Hb##	11.47	1.36	11.84	1.82	13.53	1.36	12.57	1.86	8.16	**<0.001**
WBC###	4.36	1.07	5.77	0.19	6.47	1.89	7.02	1.83	11.66	**<0.001**
ANC####	2.40	.3	3.32	0.76	3.58	0.21	3.70	0.20	5.08	**0.003**
PLT	172.13	42.87	171.27	34.97	149.65	36.05	186.13	37.34	1.62	0.19
Albumin#####	3.65	.58	3.35	.45	4.19	.83	4.12	.54	3.63	**0.02**
INR	1.13	.11	1.22	.14	1.15	.16	1.15	.09	0.93	0.43

*One Way ANOVA test
#post hoc test (group I vs group III) (group III vs group IV)
##post hoc test (group I vs group III) (group II vs group III)
###post hoc test (group I vs group II) (group I vs group III) (group I vs group IV)
####post hoc test (group I vs group III) (group I vs group IV)
#####post hoc test (group I vs group III) (group II vs group III) (group II vs group IV).

Table 8 : There were statistically significant differences between the four groups regarding T. bilirubin, Hemoglobin, White blood cells Absolute neutrophilic count and albumin while there were no statistical differences between the four groups regarding the other lab results.

Table (9): Comparison between the different regimens regarding laboratory tests at 24 weeks:

	Group I		Group II		Group III		Group IV		F*	P value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
AST	28	6.19	25.12	5.68	28.73	6.27	24.85	5.66	0.7	0.54
ALT	28.68	6.78	23.61	4.02	24.38	5.22	25.52	5.45	1.8	0.16
Total bilirubin	0.96	0.11	0.91	0.12	1.1	0.18	0.74	0.27	0.9	0.44
Direct bilirubin	0.31	0.02	0.27	0.05	0.48	0.11	0.22	0.04	0.5	0.67
Hb	13.28	1.84	12.24	1.97	13.4	2.08	12.76	1.69	2.3	0.08
WBC#	5.35	1.2	5.21	1.24	7.2	1.37	7.59	1.45	8.9	**<0.001**
ANC##	2.79	0.55	2.86	0.61	3.7	0.71	4.12	0.9	4.1	**0.01**
PLT	177.5	43.1	156.6	34.5	155.8	28.2	178.5	44	1.2	0.31
Albumin	4.01	0.59	4.22	0.61	4.44	0.87	4.43	0.41	1.2	0.31
INR	1.19	0.18	1.2	0.14	1.1	0.09	1.15	0.09	2.5	0.06

*One Way ANOVA test
#post hoc test (group I vs group III) (group I vs group IV) (group II vs group III) (group II vs group **IV)**
##post hoc test (group I vs group IV) (group II vs group IV).
Table 9: There were statistically significant differences between the four groups regarding White blood cells, Absolute neutrophilic count while there were no statistical difference between the four groups regarding the other lab results.

Table (10): Comparison between the different regimens regarding response to treatment.

		Group I		Group II		Group III		Group IV		X^{2*}	P alue
		N	%	N	%	N	%	N	%		
HCV PCR at 12 weeks	**<15**	29	93.5	20	90.9	21	91.3	29	100	3.04 Fisher exact	0.40
	>15	2	6.5	2	9.1	2	8.7	0	.0		
HCV PCR at 24 weeks	**<15**	26	78.8	28	87.5	30	96.8	35	100	10.48 Fisher exact	**0.01**
	>15	7	21.2	4	12.5	1	3.2	0	.0		
response to treatment	**cured**	26	74.3	21	60.0	30	85.7	35	100	21.15	**<0.001**
	relapse	9	25.7	14	40.0	3	8.6	0	.0		

*Chi square test

Table 10: There were statistically significant differences between the four groups regarding the response to treatment. Response was the highest in group IV (100 %) and the lowest in group I (74.3 %) and group II (60%).

Table (11): Comparison between cirrhotic (n=57) and non–cirrhotic (n=83) patients as regards type of treatment and end of treatment response.

		Cirrhotic		Non cirrhotic		X^{2*}	P value
		N	%	N	%		
Drug regimen	**Regimen I**	11	19.3	24	28.9	6.26	0.10
	Regimen II	19	33.3	16	19.3		
	Regimen III	16	28.1	19	22.9		
	Regimen IV	11	19.3	24	28.9		
	Total	57	100	83	100		
Response to treatment	**Cured**	38	69.1	74	89.1	8.10	***0.01**
	Relapse	17	30.9	9	10.9		
	Total	55	100	83	100		

*Chi square test

Table 11: There was a statistically significant difference between cirrhotic and non-cirrhotic patients as regards response to treatment (SVR being higher in non-cirrhotic 89.1% compared to in cirrhotic 69.1%).

Table (12): Comparison between naïve and experienced patients as regards type of treatment and end of treatment response.

		Naïve		Experienced		X^{2*}	P value
		N	%	N	%		
Drug regimen	**Regimen I**	26	22.2	9	39.1	16.01	**0.001**
	Regimen II	24	20.5	11	47.8		
	Regimen III	34	29.1	1	4.3		
	Regimen IV	33	28.2	2	8.7		
	Total	117	100	23	100		
Response to treatment	**Cured**	97	83.6	15	68.2	1.10	0.30
	Relapse	19	16.4	7	31.8		
	Total	116	100	22	100		

*Chi square test

Table 12: The response to treatment was higher in naïve patients when compared to experienced ones. However the difference was not statistically significant.

Table (13): Comparison between responders and relapsers as regards pre-treatment parameters in group I

	Response to treatment						t*	P value
	Cured			Relapse				
	N	Mean	SD	N	Mean	SD		
HCV PCR#	26	1740702.5	433025.6	9	207044.0	51661	2.19**	**0.03**
AST	26	41.04	9.17	9	35.74	7.46	0.79	0.44
ALT	26	37.96	20.07	9	38.11	9.47	0.02	0.98
Total bilirubin	24	.79	.15	9	.88	.10	0.81	0.43
Direct bilirubin	8	.36	.06	3	.27	.05	0.62	0.55
Albumin	26	4.09	.51	9	4.23	1.0	0.50	0.62
INR	25	1.11	.11	9	1.21	.14	2.34	**0.03**
Hb	26	14.23	1.77	9	13.94	1.35	0.45	0.66
WBC	26	6.27	1.4	9	6.51	1.50	0.29	0.77
ANC	24	3.02	0.46	7	2.87	.61	0.27	0.79
PLT	26	201.96	48.71	9	196.33	48.39	0.23	0.82
RBS	23	103.57	24.32	8	98.50	23.78	0.35	0.73
HbA1c	6	7.47	.60	1	8.70	.	1.91	0.12
Creatinine	24	.89	.19	9	.80	.11	1.72	0.10
AFP#	21	7.20	1.70	9	6.00	0.70	0.29**	0.78
TSH	19	2.15	0.45	8	.78	.05	1.04	0.31

*Independent samples t test **Mann Whitney U test (Z) #median and IQR

Table13: There were statistically significant differences between responders and relapsers as regards pretreatment HCV PCR and INR.

Table (14): Comparison between responders and relapsers as regards pre-treatment parameters in group II

	response to treatment						t*	P value
	Cured			Relapse				
	N	Mean	SD	N	Mean	SD		
HCV PCR#	21	714226.0	1109801	14	523409.5	120609	0.94**	0.36
AST	21	37.21	8.14	14	60.00	14.65	3.16	**0.003**
ALT	21	39.17	8.07	14	52.21	12.58	1.67	0.11
Total bilirubin	20	.86	.20	14	1.16	.28	2.86	**0.01**
Direct bilirubin	5	.48	.11	2	.50	.11	0.07	0.95
Albumin	20	3.99	.79	14	3.46	.54	2.17	**0.04**
INR	21	1.13	.17	14	1.20	.18	1.22	0.23
Hb	20	13.06	2.01	14	13.82	1.61	1.18	0.25
WBC	19	5.80	1.33	14	76.19	18.90	0.99	0.34
ANC	15	3.39	0.63	12	2.31	0.55	1.83	0.08
PLT	20	153.10	36.66	14	111.29	24.24	2.50	**0.02**
RBS	19	107.95	25.30	14	112.50	27.00	0.28	0.79
HbA1c	4	8.75	1.54	3	6.40	1.14	1.09	0.33
Creatinine	19	.94	.21	14	.87	.19	0.88	0.38
AFP#	20	6.95	1.63	14	9.45	2.2	1.40**	0.17

*Independent samples t test **Mann Whitney U test (Z) #median and IQR

Table14: There were statistically significant differences between responders and relapsers as regards pretreatment AST, Total bilirubin, albumin and ANC while there were no statistically significant differences between responders and relapsers as regards the other laboratory values.

Table (15): Comparison between responders and relapsers as regards pre-treatment parameters in group III

	response to treatment						t*	P value
	Cured			Relapse				
	N	Mean	SD	N	Mean	SD		
HCV PCR#	30	512009.5	1225042	3	6236442.0	1459110	1.94**	**0.05**
AST	30	48.97	11.88	3	67.00	15.17	0.90	0.38
ALT	30	57.13	13.62	3	55.67	13.01	0.06	0.95
Total bilirubin	30	.96	.23	3	1.23	.21	1.11	0.28
Direct bilirubin	6	.38	.08	2	.55	.09	0.46	0.72
Albumin	30	3.49	.49	3	3.23	.23	0.88	0.39
INR	26	1.16	.13	3	1.17	.06	0.16	0.88
Hb	30	13.39	1.67	3	14.47	.93	1.09	0.28
WBC	30	5.53	1.07	3	5.33	1.25	0.15	0.88
ANC	27	2.94	0.62	2	2.20	.42	0.84	0.41
PLT	30	153.87	37.65	3	90.00	19.16	1.82	0.08
RBS	26	119.85	28.11	3	184.33	40.99	1.76	0.09
HbA1c	3	7.17	.90	2	8.75	1.48	1.54	0.22
Creatinine	28	.88	.21	3	1.00	.23	0.92	0.37
AFP#	26	4.40	.98	3	9.40	1.50	1.43**	0.17

*Independent samples t test **Mann Whitney U test (Z) #median and IQR

Table 15: There was a statistically significant difference between responders and relapsers as regards pretreatment HCV PCR only, while there were no statistical significant difference in other laboratory values.

DISCUSSION

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide. The long-term impact of HCV infection is highly variable, ranging from minimal histological changes to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma (HCC). The number of chronically infected persons worldwide is estimated to be about 180 million, but most are unaware of their infection [(8)].

HCV seroprevalence in Egypt 2008 was estimated to be 14.7 %. Accordingly, Egypt has the highest HCV prevalence in the world [(9)] caused by extensive iatrogenic transmission during the era of parenteral antischistosomal therapy mass campaigns [(4)]. Currently, HCV is curable, unlike HIV and HBV [(5)]. Genotype 4 infects 10-15 million persons; a large percentage of whom are living in Egypt, where HCVG4 represents more than 90% of the infected population [(8)].

Clinical care for patients with HCV-related liver disease has advanced considerably during the last two decades, thanks to an enhanced understanding of the pathophysiology of the disease, and because of developments in diagnostic procedures and improvements in therapy and prevention. The primary goal of HCV therapy is to cure the infection, i.e. to achieve a sustained virological response (SVR) defined as undetectable HCV RNA 12 weeks or 24 weeks after treatment completion. The infection is cured in more than 99% of patients who achieve SVR. A SVR is generally associated with normalization of liver enzymes and improvement or disappearance of liver necroinflammation and fibrosis in patients without cirrhosis. Patients with severe liver disease remain at risk of life-threatening complications; however hepatic fibrosis may regress and the risk of complications such as hepatic failure and portal hypertension is reduced. Recent data suggest that the risk of HCC and all-cause mortality is significantly reduced, but not eliminated, in cirrhotic patients who clear HCV compared to untreated patients and non-sustained virological responders [(10)].

HCV is also associated with a number of extrahepatic manifestations and effective viral suppression induces reversal of most of them [(11)]. During the last few years, management of HCV became more effective with the appearance of different classes of direct antiviral agents (DAAs). They raised the sustained virological responses (SVR) rates from around 40% with PEGylated interferon (PEG) and ribavirin (RBV) to more than 90% [(12)].

Our study population, as the national treatment program in Egypt, included all patients ≥ 18 years old with chronic HCV infection. Although initially treatment with DAAs was prioritized to patients with advanced fibrosis (F3 and F4), starting from May 2015, patients were included with all stages of liver fibrosis (F0-F4). This study was conducted in Aswan Fever Hospital, Aswan Hospital Health Insurance and Tropical Medicine Department Ain Shams University in the period from January 2015 to July 2016.

The aim of this study was to assess the efficacy of DAAs in the treatment of HCV in Aswan Governorate and compare between different combinations of DAAs ± ribavirin ±interferon which were available during the study period as regards efficacy and the possible side effects in each treatment combination. All patients were subjected to full clinical assessment including medical history and clinical examination and laboratory investigations as complete blood count, random blood sugar, HBsAg, renal and liver functions and HCV PCR.

The patients were subdivided into four groups, the first group patients were treated with triple therapy (SOV + RBV + INF) for three months, the second group patients were treated with (SOV + RBV) for six months, the third group patients were treated with (SOV + Simeprevir) for three months and the fourth group patients were treated with (SOV + DCV ± RBV) for three months. The results of the current study were 74.3 % (26 patients) achieved SVR12 and 25.7 % (9 patients) relapsed in the first group, the main side effects in this group were anemia and hyperbilirubinemia. In the second group the SVR was 60 % (21 patients) and 40 % (14 patients) relapsed, the main side effects in this group were anemia and hyperbilirubinemia. In the third group the SVR was 85.7 % (30 patients) and 8.6 % (3 patients) relapsed and 5.7% (2 died), the main side effects in this group were anemia, hyperbilirubinemia and photosensitivity. In the fourth group the SVR was 100 % (35 patients), 15 patients in this group received Ribavirin and 20 patients without Ribavirin, the main side effects in this group were anemia, hyperbilirubinemia and photosensitivity.

In Egypt, the National Committee for the Control of Viral Hepatitis (NCCVH) started a mass treatment program that was initially based on SOF in combination with RBV for a treatment duration of 24 weeks or in combination with PEG and RBV for 12 weeks, during the period from October 2014 till May 2015, with SVR12 rates of 78.4% and 94% respectively [(13)].

Elsharkawy *et al.* [(14)] performed a study on 337,042 patients who started treatment from October 2014 to March 2016 and were grouped into three equal time intervals of 6 months each. SOF-RBV therapy for 24 weeks had the lowest SVR-12 rate (82.7%); while other therapies (as in the international program at the same period) were associated with SVR-12 rates between 94% and 98% in the same study.

In our study, the SVR12 was 60 % (21 patients) and 40 % (14 patients) relapsed in the second regimen, so it was the lowest (60 %) in comparison with other regimens which were

associated with SVR12 rates between 74% and 100 %.

ElEtreby *et al.* [15] showed a combined SOF and simeprevir (SMV) therapy that provided an overall 94%.This agreed with results of the current study SVR was 85.7 % in SOF / SMV group.

Omar et al. [16] performed a study in Egypt on patients with chronic hepatitis C. The authors reported that 18378 patients were treated with SOF + DCV ± RBV, 95.1% achieved SVR12 (95.4% among patients treated without RBV and 94.7% for patients treated with RBV).

Sulkowski et al. [17] recruited HCV-G1, 2 and 3 patients without cirrhosis who were either treatment naïve or experienced. SVR12 ranged between 89%-98% depending on genotype.

Pol *et al.* [18] reported a real-world experience for 768 HCV-G1 patients, and found an overall 95% SVR12 rate (92-99%), and that the SVR rates were not affected by treatment duration or RBV use.

Hezode *et al.* [19], in HCV-G4 patients using DCV in combination with PEG-RBV, reported that SVR24 was 100%. The ALLY-1 trial used SOF+DCV in patients with advanced cirrhosis or post-liver-transplantation and included only 4 HCV-G4 patients, who all responded to treatment [20].

Similarly, the ALLY-2 trial treated patients with HCV-HIV coinfection and included only 3 patients with HCV-G4, who all responded to treatment [22]. The ANRS-CUPILT report of treating post-liver transplant patients with SOF-DCV in France included 11 patients HCV-G4 patients, and the SVR12 rate was 91% [23].

A real-world report from Europe on compassionate use of SOF-DCV in patients with HCV and advanced liver disease included 19 HCV-G4 patients, and the SVR12 rate was 100% [24].

The previous results were close to our results in the fourth group which were 100 % (15 patients treated with ribavirin and 20 patients without ribavirin). We found that using SOF DCV, with or without RBV, led to a high SVR12 rate among a large group of HCV-G4 patients, compared to other combinations. Similar high response rates have been reported with the use of SOF plus DCV with or without RBV from real-life cohorts, even in elderly patients with several concomitant medications (though with much fewer patients) [25].

Sulkowski *et al.* [17] found that SVR12 rates did not differ after sub analysis of various factors such as sub-genotypes, IL28 phenotype, race, RBV use and history of previous treatment failure with first generation protease inhibitors. Poordad et al., 2016 found lower albumin levels associated with non-response in Child C patients as a reflection of impaired hepatic function [20].

All previous studies concluded that SOF-DCV combination is safe with limited adverse events. High incidence of serious complications (17.5%) was reported by ***Coilly et al***., as they managed HCV recurrence in transplanted patients [22]. Such patients are a peculiar situation due to multiple factors that coexist as multi drug intake, immunosuppression and possible drug-drug interactions.

In our study adverse events were limited also, and the two cases that died in the third group were due to hepatic decompensation. An important factor in this report is the sole use of generic SOF DCV in all treated patients. Although DAAs provide high cure rates, their high prices could be a barrier to rapid universal treatment uptake [25].

As the Egyptian programme for the control and eradication of HCV infection escalated, the need arose for much larger drug production at much lower costs. The MoH strongly supported local producers of generic DAAs by providing "fast track registration" of generic DAAs including SOF and DCV [23].

CONCLUSION

This is a large real-life report of the use of very low-cost generic medications for treating HCV-G4 within the largest treatment programme worldwide. The use of entirely generic SOF DCV combination with or without generic RBV was well tolerated and associated with high response rate in patients with different stages of liver disease. This can be an example for other countries of similar limited resources for managing their patients with HCV.

RECOMMENDATIONS

- Treatment with different Direct Acting Antiviral drugs combination achieves high Sustained Virological Response (SVR) among Egyptian patients with chronic hepatitis C virus (HCV).
- Treatment with Sofosbuvir and Daclatasvir (SOV + DCV) combination achieves the highest SVR.
- Mass screening should be complemented for all population especially among school children and adolescents for early detection of infection.
- Activate health education program to combat unhealthy habits as sharing the same tooth brushes and shaving tools.
- Enabling individuals for easy and possible routes of receiving antiviral therapy.
- Increasing awareness of patients who received antiviral drugs of regular follow up and measures to prevent re-infection through using personal hygienic tools.
- Allowing supportive measures for the national pharmaceutical manufacture for the production of cheap, effective and available antiviral therapy.

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