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Comparative Study between Efficacy of Two Quadruple DAAs Therapy in Treatment of HCV Relapsers

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ABSTRACT

Background: Chronic hepatitis C virus (HCV) is considered as a major cause of liver diseases. The standard treatment of HCV infection is a combination of direct-acting antiviral agents (DAAs). Relapse is defined where HCV RNA remained undetectable at the end of therapy but rebounded to pretreatment levels once DAA therapy was discontinued.

Aim of the study: This study was performed to compare efficacy and safety of two quadruple DAAs regimens (Sofosbuvir/Daclatasvir/Simeprevir and Ribavirin Vs. Sofosbuvir/Ombitasvir/ Paritaprevir/ ritonavir - Ribavirin) in treatment of HCV relapsers.

Patients and Methods: Retrospective cross-sectional study of 90 experienced patients previously treated with Sofosbuvir and Daclatasvir ± Ribavirin for 3 months and relapsed. The patients were divided into two groups, each group included 45 patients: Group I treated with (Sofosbuvir and Daclatasvir -simeprevir—Ribavirin) while Group II treated with (Sofosbuvir-Ombitasvir/Paritaprevir/ritonavir - Ribavirin).

Results: The study showed an excellent response to both regimens of treatment. In group I; the sustained virologic response rates at 24th week were 44/45 (97.8%); 100% (29/29) in non-cirrhotic and 93.8% (15/16) in cirrhotic patients. while group II SVR 24 rates were 93.3% (44/45); 92.9% (26/28) of non-cirrhotic patients, and 94.1% (16/17) of cirrhotic patients. while group II SVR 24 93.3% (44/45) of overall patients, 92.9% (26/28) of non-cirrhotic patients, and 94.1% (16/17) of cirrhotic patients. Additionally, the most common adverse events reported were easy fatiguability, headache, nausea, generalized weakness, photosensitivity - in group I only.

Conclusion: It could be concluded that the current combination regimen is well tolerated and achieved excellent SVR rates.

Keywords: two quadruple DAAs therapy, HCV relapsers.

INTRODUCTION

HCV infection causes both acute and chronic hepatitis. Incident infection is associated with early symptoms in about 20% of persons. Spontaneous clearance occurs within six months of infection in 15–45% of infected individuals in the absence of treatment. The remaining 55–85% develop chronic infection, which can lead to progressive fibrosis and cirrhosis. The risk of cirrhosis ranges from 15% to 30% after 20 years of infection with HCV [(1)].

WHO estimated that in 2015, 71 million persons were living with chronic HCV infection worldwide (global prevalence: 1%) and that 399,000 had died from cirrhosis or hepatocellular carcinoma (HCC) every year [(1)].

The highest prevalence of HCV infection is present in Egypt, with 92.5% of patients infected with genotype 4, 3.6% patients with genotype 1, 3.2% patients with multiple genotypes, and < 1% patients with other genotypes [(2)]. It should be evident that treatment failure with direct acting antiviral agents is rare, occurring in approximately 5% of patients. The most common pattern of virological failure with

DAA therapy is due to relapse, where HCV RNA remained undetectable at the end of therapy but rebounded to pretreatment levels once DAA therapy was discontinued [(3)].

The aim of the current study was to comparing efficacy and safety of two different regimens of quadruple DAAs therapies (Sofosbuvir plus Daclatasvir, Simeprevir and Ribavirin) Versus. (Sofosbuvir plus Ombitasvir, paritaprevir/ ritonavir and Ribavirin Regimen) of treatment of HCV relapsers after Sofosbuvir plus Daclatasvir with or without Ribavirin therapy.

PATIENTS AND METHODS

This retrospective cross-sectional study included a total of 90 HCV infected patients previously treated with Sofosbuvir and Daclatasvir ± Ribavirin for 3 months but detectable HCV RNA within 24 weeks of completing treatment, attending at Kafr Elsheikh Research Center of Hepatology. Written informed consent from all the subjects were obtained. This study was conducted between January 2017 to December 2017.

Ethical approval:

Current protocol was approved by the ethical committee of the Department of Tropical Medicine and Committee of Faculty of Medicine, Al-Azhar university, and then by the ethical committee, Al-Azhar university. Permission obtained from Egyptian National Committee for Control of Viral Hepatitis (NCCVH).

The patients were divided into two groups, each group included 45 patients: Group I treated with (Sofosbuvir and Daclatasvir -simeprevir—Ribavirin) while Group II treated with (Sofosbuvir-Ombitasvir/Paritaprevir/ritonavir - Ribavirin).

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***Inclusion criteria*:** All inclusion criteria were abided according to the Egyptian National HCV Control Program December 2016:

- All patients tested positive HCV RNA and previously treated with Sofosbuvir, Daclatasvir ± Ribavirin
- The age ≥18.
- Age ≥ 65 years old should undergo cardiological assessment by ECG, Echo and cardiological consultation prior to therapy.

Exclusion criteria: All exclusion criteria were abided according to the Egyptian National HCV Control Program guidelines:

1. child´s C cirrhotic patient.
2. Platelet count less than 50,000/cmm
3. HCC, except 6 months after intervention aiming at cure with no evidence of activity by dynamic imaging (CT or MRI).
4. Extrahepatic malignancy except after two years of disease-free interval, in case of lymphomas and chronic lymphocytic leukemia, treatment can be initiated immediately after remission based on the treating oncologist report, pregnancy or inability to use contraception and in adequately controlled diabetes mellitus (Hb A1c > 9 %).
5. HCV Naïve patient.

Clinical Examination: - All patients were subjected to complete history taking, which include history of other comorbid conditions such as DM, Cardiac disease and renal failure. History of previous treatment with anti-HCV medicines (e.g. peg interferon plus ribavirin, Sofosbuvir plus Ribavirin, or other combination regimens) was also evaluated. Sensitivity to any other drug had to be checked out, full clinical examination: which include manifestations of chronic liver disease (such as jaundice, flapping tremors, lower limb edema, organomegaly, ascites) and obesity (BMI).

Laboratory Investigations: complete blood count (CBC), alanine aminotransferase (ALT,), aspartate aminotransferase (AST), albumin, total bilirubin & direct bilirubin, prothrombin time and INR, creatinine, urea, Alpha Fetoprotein (AFP), PCR at baseline (day 0).

Imaging: Patients were submitted to screening with the following procedures: Abdominal Ultrasonography: which include; liver size, echogenicity, portal and splenic vein diameters, splenic size, amount of ascites if present.

Treatment dose and period: : Group I treated with (Sofosbuvir 400mg One tablet once daily, Daclatasvir 60 mg One tablet once daily -Simeprevir 150 mg One tablet once daily -Ribavirin 200 mg Two capsules in the morning and 3 in the evening if body weight <75 kg or Three capsules in the morning and 3 in the evening if body weight ≥75 kg (or less if dose reduction needed) for 12 weeks.

while Group II treated with (Sofosbuvir 400mg One tablet once daily. Ombitasvir – Paritaprevir- Ritonavir (Tablets containing 12.5 mg of Ombitasvir, (75 mg of paritaprevir and 50 mg of ritonavir) Two tablets once daily – Ribavirin 200 mg Two capsules in the morning and 3 in the evening if body weight <75 kg or Three capsules in the morning and 3 in the evening if body weight ≥75 kg (or less if dose reduction needed) for 12 weeks.

Monthly follow up: All patients were submitted to the following investigations every 4 weeks; Routine clinical examination, laboratory investigation: CBC, ALT, AST, Bilirubin. Real time HCV PCR at the 24th week after end of treatment.

Data interpretation

Sustained Virologic Response (SVR)and safety of different regimens. Data handling by Biostaticain.

Statistical Analysis: Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

This study was aimed to Compare the efficacy and safety of two regimens of quadruple therapies (Sofosbuvir and Daclatasvir -Simeprevir- Ribavirin versus Sofosbuvir-Ombitasvir /Paritaprevir/Ritonavir-Ribavirin) of treatment of HCV relapsers after Sofosbuvir and Daclatasvir +/ Ribavirin therapy.

From January 2017 to December 2017. Ninety patients were enrolled and treated at Kafr Elsheikh Research Center of Hepatology, Egypt. The patients were divided into two groups, each group studied included 45 patients:

Group I: SOF-SIM-DAC-RBV **26** males (57.8%) versus 19 females (42.2%) with mean age 50.09 while **Group II**: SOF-OMP-PAR-RBV included 29 males (64.4%) versus 16 females (35.6%) with mean age 52.00. Also, mean BMI was 27.78 in **Group I** studied while was 27.21 in **Group II.**

Group I and **Group II** samples showed no statically significant differences in components of complete blood count before receiving treatment. Mean values of HB were 13.36 and 13.88 in both groups respectively with p value (0.123). While in WBCs they were 5950 and 6750 in both groups respectively with p value (0.046). In platelets they were 170840 and 166730 in both groups respectively with p value (0.777).

In Group I, mean values of **HB** before and after treatment were 13.36, 11.58 g/dl respectively**. In Group II** mean values of HB before and after treatment were 13.88, 11.76 g/dl respectively. So, there is significant correlation between receiving theses quadruple therapies and decrease of HB (P value < 0.001) **and** (P value < 0.001) of **Group I and Group II** respectively.

Table (1): Comparison between both groups according to baseline data. This shows no statistically significant

difference between groups according to demographic data.

Demographic Data	Group I: SOF-SIM-DAC-RBV *(n=45)*	Group II: SOF-OMP-PAR-RBV *(n=45)*	t/x2#	p-value
Age (years) Mean±SD Range	 50.09±8.89 32_67	 52.00±11.01 21_78	0.821	0.367
Gender Male Female	 26 (57.8%) 19 (42.2%)	 29 (64.4%) 16 (35.6%)	0.421 #	0.517
BMI [wt(ht)/^2] Mean±SD Range	 27.78±4.84 21_45	 27.21±5.61 6.4_34	0.273	0.602

t-Independent Sample t-test; #x^2: Chi-square test
p-value >0.05 NS

Table (2): Comparison between groups according to albumin, INR, creatinine, Fib4 calculation and alpha fetoprotein. This shows no statistically significant difference between groups according to Albumin (g/dl), INR, Creatine (mg/dl) and degree of fibrosis.

	Group I: SOF-SIM-DAC-RBV *(n=45)*	Group II: SOF-OMP-PAR-RBV *(n=45)*	t-test	p-value
Albumin (g/dl) Mean±SD Range	 4.08±0.70 3.1_7.6	 3.95±0.47 3_5.2	1.131	0.291
INR Mean±SD Range	 1.00±0.21 0.5_1.5	 1.04±0.16 0.6_1.4	0.615	0.435
Creatinine (mg/dl) Mean±SD Range	 0.82±0.18 0.4_1.1	 0.93±0.54 0.4_ 1.45	1.296	0.198
Fib4 Calculation Mean±SD Range	 2.89±2.30 0.49_9.24	 2.93±2.66 0.51_15.51	0.006	0.937
AFP (units) Mean±SD Range	 13.06±2.74 5-20	 14.01±2.96 6-19	1.580	0.118

Table (3): Comparison between laboratory data before and after treatment (at end of treatment) in group I: SOF-SIM-DAC-RBV (n=45). This shows statistically significant difference between groups according to Hb, total bilirubin, ALT and AST

Group I: SOF-SIM-DAC-RBV *(n=45)*	Before	After	Diff.	Paired t-test	p-value
Hb (g/dl)	13.36±1.63	11.58±1.62	-1.77±2.15	5.515	<0.001**
Plateletsx10^3/mm^3	170.84±73.67	179.78±99.49	8.93±78.92	-0.759	0.452
WBCx10^3/mm^3	5.95±1.60	5.67±2.11	-0.28±2.04	0.927	0.359
Total Bilirubin (mg/dL)	0.87±0.35	1.38±0.71	0.51±0.72	-4.763	<0.001**
ALT (IU/L)	34.11±14.14	28.18±11.30	-5.93±3.66	10.862	<0.001**
AST (IU/L)	32.42±14.02	26.82±11.07	-5.60±3.60	10.430	<0.001**

t-Paired Sample t-test
*p-value >0.05 NS; *p-value <0.05 S; **p-value <0.001 HS*

Table (4): Comparison between laboratory data before and after treatment in group II: SOF-OMP-PAR-RBV (n=45). This shows statistically significant difference between groups according to Hb, total bilirubin, WBC, ALT and AST.

Group II: SOF-OMP-PAR-RBV *(n=45)*	**Before**	**After**	**Diff.**	**Paired t-test**	**p-value**
Hb (g/dl)	13.88±1.59	11.76±1.55	-2.12±2.48	5.740	<0.001**
Plateletsx10^3/mm^3	166.73±63.26	181.40±54.20	14.67±76.22	-1.291	0.204
WBCx10^3/mm^3	6.75±2.13	5.54±2.09	-1.21±3.13	2.604	0.013*
Total Bilirubin (mg/dL)	0.89±0.34	1.31±0.60	0.42±0.69	-4.116	<0.001**
ALT (IU/L)	32.58±10.00	26.91±8.44	-5.67±2.83	13.440	<0.001**
AST (IU/L)	33.60±11.46	27.73±9.21	-5.87±3.21	12.263	<0.001**

t-Paired Sample t-test
*p-value >0.05 NS; *p-value <0.05 S; **p-value <0.001 HS.*

Table (5): Comparison between groups according to PCR(SVR 24) in cirrhotic and non cirrhotic patients. This shows no statistically significant difference between groups according to PCR in cirrhotic and non cirrhotic patients

PCR After(at 24th week)	**Group I: SOF-SIM-DAC-RBV *(n=45)***	**Group II: SOF-OMP-PAR-RBV *(n=45)***	**X2**	**p-value**
Cirrhotic Negative Positive	 15 (93.8%) 1 (6.3%)	 16 (94.1%) 1 (5.9%)	 0.470	0.493
Non Cirrhotic Negative Positive	 29 (100.0%) 0 (0.0%)	 26 (92.9%) 2 (7.1%)	 0.555	0.456

Table (6): Adverse events after retreatment (SOF-OMP-PAR-RBV) Vs. (SOF-SIM-DAC-RBV) of patients. This shows no statistically significant difference between groups

Side effect Overall patients	**Group I: SOF-SIM-DAC-RBV *(n=45)***		**Group II: SOF-OMP-PAR-RBV *(n=45)***		**Chi-square test**	
	No.	**%**	**No.**	**%**	**x^2**	**p-value**
Patients	45	100.0%	45	100.0%	0.000	1.000
Any adverse event during treatment	38	84.4%	35	77.8%	0.281	0.596
Adverse event leading to discontinuation	0	0.0%	0	0.0%	0.000	1.000
Serious adverse events	0	0.0%	0	0.0%	0.000	1.000
Common AEs						
fatigue	16	35.6%	12	26.7%	0.468	0.494
Headache	11	24.4%	15	33.3%	0.489	0.485
Nausea	14	31.1%	11	24.4%	0.225	0.635
Vomiting	3	6.7%	5	11.1%	0.132	0.717
Asthenia	15	33.3%	13	28.9%	0.050	0.823
Abdominal trouble	12	26.7%	6	13.3%	1.757	0.185
Pruritus	3	6.7%	3	6.7%	0.000	1.000
Insomnia	5	11.1%	5	11.1%	0.000	1.000
Photosensitivity	3	6.7%	0	0.0%	1.393	0.238
Irritability	4	8.9%	6	13.3%	0.108	0.742

x^2: Chi-square test
*p-value >0.05 NS; *p-value <0.05 S*

DISCUSSION

This decrease in HB level is probably due to ribavirin and this is with agreement with ***Fried et al.*** [4] that found that Ribavirin causes a dosage-dependent hemolytic anemia ribavirin (1000-1200 mg/2day). In addition, ribavirin-associated anemia, in recent studies, appears to be much lower than seen in the past, may be due to the absence of the bone marrow-suppressant effects of peg-INF-α. [5].

we found a significant decrease in the WBC count in **group II** only (6.75-5.54×103/mm3) before and after treatment respectively P value= (0.013). **Tong et al** [6] allocated 128 patients with chronic HCV infection (30.5% had compensated cirrhosis) into 4 groups. In the group that was treated with SOF/RBV for 24 weeks neutropenia developed only in 19.4% (12/62) of patients.

In our study, the decrease in the mean WBC count in Group II was in agreement with the results reported by **Elsharkawy *et al*.** [7], who found a significant decrease in the WBC count in 8 Egyptian patients with cirrhosis treated with SOF/RBV for 24 weeks with a mean difference in the mean WBC count of -1.84×103/mm3 between pretreatment and the end of treatment. However, in the same study 17 patients with cirrhosis treated with SOF/DAC ± RBV had a non-significant increase in the mean WBC count of 0.18×103/mm3 at the end of treatment compared to the pretreatment mean WBC count, which was inconsistent with our results.

In both groups of the current study, a significant decrease in the mean levels of transaminases (AST and ALT) during treatment. (P value= <0.001) was found.

This occurred in **Group I** as follow: mean values of **ALT** before and after treatment were (32.5- 26.91) respectively. While those of **AST** before and after treatment were (33.60- 27.73) respectively (Table 3). In group II mean values of **ALT** before and after treatment were (32.58 - 26.91) respectively. While those of AST before and after treatment were (33.60 - 27.73) respectively (Table 4). According to Total Bilirubin; mean values were before and after treatment were 0.87, 1.38 mg/dl and 0.89,1.31mg/dl in **Group I** and **Group II** respectively that statistically significant difference between groups. So, there is significant correlation between receiving these quadruple therapy and hyperbilirubinemia (P value <0.001).

In agreement with our results, **Hézode *et al.*** [8] that showed increase in serum conjugated bilirubin level with Sofosbuvir-Daclatasvir-Simeprevir Plus Ribavirin in Direct-Acting Antiviral–Experienced Patients with Hepatitis C. Also, **EASL** [9] recommended that the adverse reactions with patients receiving simeprevir mild, transient hyperbilirubinemia not accompanied by changes in other liver parameters was observed in approximately 10% of cases.

In patient who received SOF/OBV/PTV/r + RBV hyperbilirubinemia **Shafran *et al*.** [10] showed that 1/21 patient who received SOF/OBV/PTV/r + RBV developed hyperbilirubinemia. This finding can be explained by RBC haemolysis due to RBV, which leads to an increase in the mean indirect bilirubin level. This finding was in agreement with those of **Abd-Elsalam et al.** [11], who found a significant increase in the mean total bilirubin level of 1.7 mg/dl during treatment of 2400 Egyptian patients with cirrhosis treated with SOF/RBV for 6 months. However, this finding was not in agreement with those of **Elsharkawy *et al.*** [12] who reported that 12 Egyptian patients with cirrhosis who received SOF/DAC ± RBV for 12 weeks and 37 Egyptian patients with cirrhosis who received SOF/RBV for 24 weeks developed a non-significant increase in the mean total bilirubin level at the end of treatment. As regards to response to treatment in our study, high rates of SVR were observed in treatment-experienced patients receiving SOF with DCV/SMV plus RBV was 44/45 (97.8%) SVR24 rates were 100% (29/29) and 93.8% (15/16) in non-cirrhotic and cirrhotic patients, respectively.

In agreement with our finding, **Abdel-Moneim *et al.*** [13], found that 97% (89/92) of patients who received SOF/DCV/SMV plus RBV achieved SVR12. SVR12 rates were 99% (70/71) and 91% (19/21) in non-cirrhotic and cirrhotic patients, respectively.

Also, **Lawitz *et al*.** [14] concluded that 12-week treatment of SOF/DCV/ SMV was safe and well tolerated, and achieved 100% SVR12 in cirrhotic patients with portal hypertension or decompensated liver disease. Also, **Hézode *et al*.** [8], reported that 60% of DAA experienced patients treated with combination of SOF/DCV/ SMV plus RBV achieved SVR at 12 weeks. The study included a small group of 12 patients only.

On the other hand, the efficacy results clear that patients retreated with SOF/OBV/PTV/r + RBV achieved an excellent SVR24 rate; 93.3% (44/45) of overall patients, 92.9% (26/28) of non-cirrhotic patients, and 94.1% (16/17) of cirrhotic patients.

In agreement with our finding, the QUARTZ II-III study investigated the strategy of combining three DAAs: SOF + OBV/PTV/r with or without RBV in treatment-naïve patients with HCV genotype 2 or genotype 3 infection without cirrhosis or with compensated cirrhosis. The combination regimen of SOF+OBV/PTV/r with RBV for 8 weeks revealed that SVR12 rate was achieved by 90% in patients with genotype 2 infection. Moreover, the treatment for 12 weeks with SOF +OBV/PTV/r ± RBV achieved SVR12 by 98% of patients with genotype 3 infection [9]. Additionally, **Flisiak *et al*.** [15] reported, in real-world evidence, an excellent antiviral potency of OBV/PTV/r/dasabuvir (DSV)/ RBV in the treatment of HCV GT1 and 4, the SVR12 was achieved by 99% (207/209) of overall patients, the SVR12 rates ranging from 96 to 100% across subgroups. Also, **Wedemeyer *et al.*** [16], in another trial, concluded that OBV/PTV/r +DSV ± RBV regimen demonstrated high rates of SVR12 in clinical trials for the treatment of HCV GT 1 and 4. The overall SVR12 rates were 96.8% for GT1 and 98.9% for GT4.

The safety profile of the current DAAs combination regimen was favorable, and tolerability of regimen was mostly mild or moderate in our patient cohort. The main

Side effects were Fatigue (35.6-26.7%), headache (24.4-55.6%), Asthenia (53.3-37.8%), pruritus (6.7 - 6.7%), Photosensitivity (6.7%-0.0%), Irritability (8.9- 13.3%) in Group I and Group II respectively.

Other S/E vomiting (6.7-11.1%), abdominal trouble (26.7-13.3%), in Group I and Group II respectively **(table 6).** There were no deaths recorded, no serious AEs were reported and no discontinuation of the treatment.

Also **Abdel-Moneim *et al*. [(5)]** Concerning safety and tolerability of SOF/SIM /DCV plus RBV, adverse events were reported in 64 patients (70%) and generally were mild and transient. The most common AEs observed across all treatment arms during and after 12 weeks of follow-up included fatigue (24%), headache (21%), asthenia (19%), nausea (12%), and abdominal troubles (11%). There were no deaths recorded, and only three serious adverse events were reported but did not cause discontinuation of the treatment

large study (327 patients) that reported that the main S/E of SOF +OBV/PTV/r + RBV were fatigue (59%), headache (36%), nausea (34%) and insomnia (25%). **Shafran *et al.* [(9)]** reported that the most common adverse events observed in patients of GT2 and GT3 received OBV/PTV/r + SOF ± RBV for 12 weeks were fatigue and headache. **Andreone *et al.* [(17)]** reported that although ribavirin is mainly associated with pruritus, asthenia, and insomnia, most of these adverse events were mild in severity. In addition, ribavirin-associated anemia, in recent studies, appears to be much lower than seen in the past, may be due to the absence of the bone marrow-suppressant effects of peg-INF-α. Also **Abdel-Moneim *et al*. [(13)]** the most common adverse events observed across all treatment arms during and after follow-up for 12 weeks included a headache (22%), fatigue (20%), asthenia (18%), dyspnea (17%), nausea (14%), and abdominal troubles (13%). Moreover, a decrease in hemoglobin concentration (11%) was recorded. The data revealed that there were no deaths and discontinuations recorded due to serious adverse events that showed in four treated patients (inpatient hospitalization due to anemia).

CONCLUSION

The current combination regimen was well tolerated and achieved excellent SVR rates. The choice of combining multiple DAAs with different viral targets may be an effective treatment strategy in treatment HCV relapsers.

RECOMMENDATIONS

Further studies should be done to evaluate efficacy of these regimens of DAAs in HCV relapsers.

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