Egyptian Journal of Medical Microbiology Volume 29 / No.2 / April 2020 137-144 Online ISSN: 2537-0979

ORIGINAL ARTICLE

Biochemical Hepatic Changes in Chronic Hepatitis C Patients Induced by Sofosbuvir and Daclatasvir with or without Ribavirin Regimens

[1]Rashed M. Hasen, [1]Nagla Abd Al Monem, [1]Kamal A. Amer, [2]Manal M.El-Gerby*
[1]Tropical Medicine Faculty of Medicine - Zagazig University-Egypt
[2]Clinical Pathology Department, Faculty of Medicine - Zagazig University-Egypt

Key words:
Biochemical, Chronic Hepatitis C, Sofosbuvir, Daclatasvir, Ribavirin Regimens

Corresponding Author:
Manal Mohammed El -Gerby
Clinical Pathology Department, Faculty of Medicine - Zagazig University-Egypt
Tel.: 01121694422
manalelgerby@yahoo.com

ABSTRACT

Background: *Huge efforts have been made to control chronic HCV in Egypt with appearance of Direct-Acting Antivirals (DAAs) with their anticipated excellent efficacy and tolerability.* ***Objectives****: This work is evaluating the effect of DAA regimens (SOF/DAC with or without RBV) on liver biochemical profile and hematological indices during and after treatment.* ***Methodology:*** *184 patients were included in this study, the patients were divided equally according to National Committee for Control of Viral Hepatitis protocol update on November 2015 (NCCVH , 2015a) into two groups treated by 2 regimens (SOF/DAC with or without RBV) according to their classification easy to treat or difficult to treat. The patients were followed up through treatment by clinical evaluation, CBC, liver functions and kidney functions after 2 weeks and 1 week (if receiving RBV) of treatment then every month till end of treatment and after 3 months of treatment stoppage. PCR for HCV RNA in week 16 [End Of Treatment (EOTR)] and 3 months after stoppage of therapy (week 24).* ***Results:*** *The mean age was 49 years. 58.7% were males, 41.3% were females , all of them were treatment-naïve and cirrhotic and the SVR12 rate was 94.6% without RBV and 100% with RBV regimen. Decline in ALT and AST occurred after treatment, with no change in ALB and no decrease in white blood cells in both treated groups. A rise in BIL and INR additionally, drop in hemoglopin and platelets in patients receiving (SOF/DAC/RBV) regimen .However, patients who received (SOF/DAC) showed improvement in INR and platelets.* ***Conclusion*** *Daclatasvir plus sofosbuvir with or without ribavirin for 12 weeks is highly effective in treatment of naïve Egyptian patients and improve hepatitis process caused by viral infection that was evidenced by decreased liver enzymes level (AST,ALT). However, Cirrhotic patients who add RBV still require careful observation as they are more susceptible for treatment related complications .*

INTRODUCTION

Hepatitis C virus is a significant public health problem and the leading cause of hepatocellular carcinoma and liver transplantation worldwide[1]. The prevalence of hepatitis C virus (HCV) in Egypt was about 14.7% according to Egypt demographic health survey (EDHS)[2] ,this prevalence is markedly decreased in 2015 , the prevalence of HCV antibody was found to be 10.0% , and that of HCV RNA to be 7.0% in the 15-59 age group according to EGYPT HEALTH ISSUES SURVEY[3] .

More than 90% of infections are genotype 4.It is thought to be related to mass parentral antischistosomal therapy[4].

The goal of HCV treatment is sustained virological response (SVR) which is defined as the continued absence of detectable HCV RNA at least 12 weeks after completion of therapy[5].

Recently there have been a lot of trials with different direct acting antiviral agents (DDAS) oral regiments showing increased SVR rates , good tolerability and less duration of treatment[6] .

Sofosbuvir has an excellent tolerability and safety profile, most adverse effects have been noticed in sofosbuvir combination with RBV and or IFN[7].

Daclatasvir is a first class in HCV NS5A replication complex inhibitor. Daclatasvir is active at picomolar concentration in vitro in HCV replicons expressing a broad range of HCV genotypes and act in an additive to synergistic fashion with other DDAS[6].

Ribavirin as a single agent has no significant effect on HCV RNA levels, despite observations of improvements in serum aminotransferase levels and liver histology using ribavirin with interferon or peginterferon, significantly reduces relapse rates and causing significant improvement in SVR. Utility of ribavirin in interferon-free regiments enhanced antiviral

activity, delay the resistance, and resulted in a greater proportion of patients achieving a rapid SVR**.** Ribavirin can cause severe anemia so dose adjustement is required[8]**.**

Several studies have followed patients for clinical, virologic, and biochemical outcomes for up to ten years after SVR. Comparisons among these studies are limited by differing patient populations, treatment regimens, and HCV RNA detection methodologies, Infrequent late virologic relapse has been reported[9]**.**

METHODOLOGY

Patient Population

This is a prospective cohort study was conducted at Tropical Medicine Department and Clinical Pathology Department, Zagazig University Hospitals in the period between March 2017 and August 2017. Consent was obtained from each patient and approval of the ethical committee was obtained.

184 patients were included. In this study, the patients were divided according to National Committee for Control of Viral Hepatitis protocol update on November 2015NCCVH,[10] into two groups:

- ***Group I:*** Included 92 naïve patients receiving (sofosbuvir + daclatasvir) for 12 weeks. Sofosbuvir 400 mg once daily orally and Daclatasvir 60 mg once daily orally.
- ***Group II:*** Included 92 naïve Patients receiving (sofosbuvir + daclatasvir + ribavirin) for 12 weeks

Sofosbuvir 400 mg once daily orally, Daclatasvir 60 mg once daily orally and Ribavirin started by 600 mg daily in two divided doses (200,400) mg increasing according to patient tolerability.

Treatment regimen:

Inclusion criteria:

Patients with chronic HCV infection evidenced by +ve HCV RNA quantitative PCR with at least twice elevation of liver enzymes (more than 2 upper limits) in the previous 6 months without cirrhosis or with compensated cirrhosis (Diagnosis of cirrhosis was based on clinical examination, laboratory investigations and imaging techniques) and were classified according to NCCVH 2015 to:

Easy to treat group (Group I): Treatment naïve. Total serum bilirubin <1.2 mg/dl. Serum albumin ≥ 3.5 gm/dl. INR <1.2. Platelet count ≥ 150.000/mm³. Treatment with Daclatasvir 60mg once daily plus Sofosbuvir 400 mg once daily for 12 weeks.

Difficult to treat group (Group II): Peg-IFN treatment experienced.Total serum bilirubin ≥ 1.2 mg/dl. Serum albumin <3.5 gm/dl. INR ≥ 1.2. Platelet count <150.000/mm³. Treatment with Daclatasvir 60mg once daily plus Sofosbuvir 400 mg once daily plus Ribavirin started by 600 mg daily in two doses for 12 week .

Exclusion Criteria:

Any of the following: Total serum bilirubin > 3mg/dl. Serum albumin <2.8 gm/dl. INR ≥1.7. Platelet count<50000/mm³. HCC except 4 weeks after intervention aiming at cure with no evidence of activity by dynamic imaging (CT or MRI) and extra hepatic malignancy. Extra hepatic malignancy except after 2years of disease-free interval. In cases of lymphomas and chronic lymphocytic leukemia, treatment can be initiated immediately after remission based on the treating oncologist report. Pregnancy or inability to use effective contraceptive. Inadequately controlled diabetes mellitus (HbA1c>9%).Age below 18 years or over 75 years.

All patients were subjected to:

Full history taking, complete general examination local examination, examination of chest, heart, CNS and abdomen.

Investigations including:

a- *Laboratory investigations*:

Complete blood picture (CBC).Liver profile(S. bilirubin, SGOT, SGPT, ALP, total protein and S. albumin).Coagulation profile(PT, PTT and INR). Kidney profile:(S. creatinine, Bl. Urea).Viral markers (Hepatitis B surface antigen (HBsAg) & HBc IGM .Hepatitis C immunoglobulin G (HCV IgG).Alpha-feto protein (α-FP).Blood sugar and HBA1C for diabeticsHCV PCR using the COBAS® TaqMan® HCV Test v2.0.

Imaging studies:

- *Abdominal ultra-Sonography (U/S):*

Ultrasound is a major screening tool for cirrhosis and its complications. Sonoscape S11 machine with a transducer of 3.5 MHz was used. Appearances include: Surface nodularity: (88% sensitive, 82-95% specific) [11], overall coarse and heterogeneous echotexture.Segmental hypertrophy/atrophy,caudate width: right lobe width >0.65 (43-84% sensitive, 100% specific) [11],reduction of the transverse diameter (<30 mm) of the medial segment of the left lobe (segment IV) [12]**,**signs of portal hypertension:Increased portal vein diameter: >13 mm (42% sensitive, 95-100% specific[13]**,** Portal vein thrombosis, portosystemic collaterals, splenomegaly, ascites

Follow up:

- Patients were followed up through treatment by clinical evaluation, CBC, liver functions and kidney functions after 1 week and 2 weeks of treatment then every month till end of treatment and PCR for HCV RNA in week 16 [End Of Treatment (EOTR)] and 3 months after stoppage of therapy (week 24).
- The primary efficacy end point was the percentage of patients in each group with SVR, defined as HCV RNA < 15 IU/mL 12 weeks after stoppage of treatment [14].
- Patients in all groups were followed up monthly during treatment and for 3 months after end of treatment for any developed adverse effects with complete analysis including onset, course, duration, association, frequency, if the patient asked for medical

advice, took any medications and if had been admitted to hospital for these side effects.

- Grading of these adverse effects was done according to the common terminology criteria of adverse events 2010 *(CTCAE, 2010)* [15].

Statistical Analysis

The data were tabulated and statistically analyzed using and SPSS version-24 software package. Data were tested for normal distribution using the Kolmogorov–Smirnov test.Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$) and Fisher exact was used to calculate difference between qualitative variables as indicated. Quantitative data were expressed as mean ± SD (Standard deviation) for parametric and median and range for non-parametric data. One-way ANOVA F-test and Kruskal-Wallis Test were used to calculate difference between quantitative variables in more than two groups in normally normal and non-parametric variables respectively.

RESULTS

This study included 272 HCV genotype 4-infected patients, who received SOF/DAC with o without RBV regimens.

Age of patients ranging from 32 to 61 years old with median 49 years old, 108 male(58.7 %) and 76 female(41.3%), all patients were cirrhotic, table 1 show a high significant difference between values of platelets, white blood cells, billirubin, albumin, INR, serum ALT and AST between the two groups but there was no significant difference between them in values of serum creatnine and hemoglobin before treatment.

Table 1: Comparison between baseline lab values in both group

Baseline		Regimen (Group1)	Regimen (Group 2)	T-Test	P
CBC	Hb, g/dl N(11.5:15.5g/dl)	12.3 ±1.3	11.9 ± 1.2	1.7	0.092
	PLT, x10^9L N(150-450 10^9L)	198.1 ±32.7	130.4 ± 19.7	17.0	<0.001
	WBC, x103L N(4,000-11,00010^{6}L)	6244.8 ±1309.1	5797.8 ± 1326.4	2.3	0.023
LFTs	Bil, mg/dl (Up to- 1.2 mg/dl)	1.1 ± 0.1	2.2 ± 0.4	-24.3	<0.001
	Alb, mg/dl N (3.5- 5.2 g/dl)	3.9 ± 0.2	3.2 ± 0.2	20.2	<0.001
	INR (0.8- 1.2)	1.1 ± 0.1	1.4 ± 0.1	-16.0	<0.001
	ALT, IU/l (Up to- 40 U/L)	35.1 ± 12	103.8 ± 18.8	-29.6	<0.001
	AST, IU/l (Up to- 41 U/L)	33.5 ± 9.4	107.2 ± 30.7	-22.0	<0.001
Cr, mg/Dl (0.7- 1.2 mg/dl)		0.7 ± 0.2	0.7 ± 0.2	-1.9	0.054

Data are presented in mean and standard deviation
*significant p value ≤ 0.05

Comparison between baseline HCV RNA PCR of the studied groups table 2 clearing that statistically high significant difference was present among both of them . SVR was 100% in group 1 and 2 in wk 16 .However, it becomes 94.6% in group 1 and 100% in group 2 in wk 24 as there was 5 patients showing treatment failure in group 1.

Table 2: Baseline and serial follow up PCR value between groups

		Regimen (Group1) SOF/DAC	Regimen (Group2) SOF/DAC/RBV	Kruskal-Wallis Test	P
Base line PCR • Median • Range		2144470 (4500-245879324)	353465 (55-513336760)	-3.7	**<0.001**
		N (%)	**N (%)**	**X^2**	**P**
PCR.M4	Negative	100 (100.0%)	100 (100.0%)	------	------
	Positive	0 (0.0%)	0 (0.0%)		
PCR.M6	Negative	87 (94.6%)	92 (100.0%)	5.3	0.059
	Positive	5 (5.4%)	0 (0.0%)		

The changes in Laboratory parameters before and after SOF/ DAC therapy can be demonstrated in table 3.There was statistically high significant difference of platelets count, white blood cells, bilirubin, albumin, INR and liver enzymes of patients receiving (SOF/DAC) towards improving but there was no difference in hemoglobin or creatinin levels . However , statistically high significant reduction of hemoglobin, platelets , serum albumin, serum ALT and serum AST values before and at end of therapy in group (2)who received (SOF/DAC/RBV) and also showed statistically high significant increasing of billirubin levels table 4 .

Table 3: The changes in Laboratory parameters before and after SOF/ DAC Therapy (Group 1)

	SOF/DAC (Group1)		T	p
	Baseline before Therapy	End of Therapy		
Hb, g/dl	12.3 ± 1.3	12.3 ± 1.2	-1.9	0.057
PLT, x10^9L	198.1 ± 32.7	226.5 ± 40	-7.8	<0.001
WBC, x103L	6244.8 ± 1309.1	7722.8 ± 1254.6	-8.1	<0.001
Bil, mg/dl	1.1 ± 0.1	0.9 ± 0.1	-6.2	<0.001
Alb, mg/dl	3.9 ± 0.2	4 ± 0.2	-6.0	<0.001
INR	1.1 ± 0.1	1 ± 0.1	-7.2	<0.001
ALT, IU/l	35.1 ± 12	29.8 ± 9.3	-6.2	<0.001
AST, IU/l	33.5 ± 9.4	29.6 ± 7.9	-5.8	<0.001
Cr, mg/dL	0.7 ± 0.2	0.7 ± 0.2	1.0	1.000

Table 4: The changes in laboratory parameters before and after SOF/ DAC/RBV Therapy (Group 2)

	SOF/DAC/RBV (Group 2)		T	P
	Baseline before Therapy	End of Therapy		
Hb, g/dl	11.9 ± 1.2	11.5 ± 0.8	-4.2	<0.001
PLT, x10^9L	130.4 ± 19.7	107 ± 24.1	-8.1	<0.001
WBC, x103L	5797.8 ± 1326.4	10548.9 ±1511.8	-8.3	<0.001
Bil, mg/dl	2.2 ± 0.4	2.3 ± 0.4	-2.5	0.011
Alb, mg/dl	3.2 ± 0.2	3.1 ± 0.2	-4.8	<0.001
INR	1.4 ± 0.1	1.4 ± 0.1	-0.5	0.567
ALT, IU/l	103.8 ± 18.8	79.1 ± 16.9	-8.1	<0.001
AST, IU/l	107.2 ± 30.7	61.1 ± 10.2	-8.3	<0.001
Cr, mg/dL	0.7 ± 0.2	0.7 ± 0.2	1.0	1.000

Data are presented in mean and standard deviation
*significant p value ≤ 0.05

Comparison between the degree of changes in Hemogram and Liver Disease Parameters before and after treatment in both group is shown in table 5. There was a high statistically significant difference as decreasing in values of platelets and albumin, increasing values of billirubin and INR in group 2.

Table 5: Comparison between the degree of changes in Hemogram and Liver Disease Parameters before and after treatment in both group

	Regimen		t	Sig.
	SOF/DAC (Group1)	SOF/DAC/RBV (Group 2)		
Hb, g/dl	0.1 ± 0.5	-0.4 ± 0.9	4.8	<0.001
PLT, x109L	28.4 ± 25.1	-23.4 ± 16.3	16.6	<0.001
WBC, x109L	1478 ± 866.2	4751.1 ± 1645.8	-16.9	<0.001
Bil, mg/dl	-0.1 ± 0.1	0.1 ± 0.4	-5.7	<0.001
Alb, mg/dl	0.1 ± 0.1	-0.1 ± 0.1	9.4	<0.001
INR	-0.1 ± 0.1	0 ± 0.1	-8.3	<0.001
ALT, IU/l	-3.7 ± 4.6	-28.1 ± 21.2	10.8	<0.001
AST, IU/l	-5.5 ± 7.9	-42.7 ± 18.2	18.0	<0.001
Cr, mg/dL	0 ± 0	0 ± 0	-	-

Data are presented in mean and standard deviation
*significant p value ≤ 0.05

Comparison of clinico-demographic Findings and baseline laboratory values between patients who achieved and did not achieve SVR table 6 showed that there is no significant difference between them in age, sex and child score. However , There is a significant difference between them in base line values of platelets count, serum billirubin and serum ALT.

Table 6: Comparison between baseline laboratory values between patients who achieved and did not achieve SVR

Baseline Lab.	SVR		Test	P
	Achieved N=179	Did not achieve N=5		
Hb, g/dl	12.2 ± 1.7	12.1 ± 1.3	0.2	0.848
PLT, x10^{9}L	216.2 ± 40.2	162.8 ± 42.6	2.8	0.006
WBC, x103L	5960 ± 981.3	6023 ± 1343.7	-0.1	0.917
Bil, mg/dl	1 ± 0.2	1.7 ± 0.7	-2.1	0.035
Alb, mg/dl	3.9 ± 0.1	3.5 ± 0.4	1.8	0.072
INR	1.1 ± 0.1	1.2 ± 0.2	-1.8	0.082
AST, IU/l	33.8 ± 7	71.4 ± 43.5	-1.9	0.056
ALT, IU/l	33.6 ± 12.6	70.5 ± 37.9	-2.2	0.031
Cr, mg/dL	0.6 ± 0.2	0.7 ± 0.2	-1.1	0.280
PCR	2103658 (500000-14523400)	1215422 (55-513336760)	-0.5	0.615

Data are presented in mean and standard deviation
*significant p value ≤ 0.05

DISSCUSSION

In this work, the hepatic related biochemical effect after sofosbuvir + daclatasvir with or without RBV was evaluated among patients with CHC .

As regards clinicodemographic data including age and sex no statistically significant difference was present between the studied groups . Also, in the current study there was 108 male (58.7%) and 76 female (41.3%).The male predominance highlighted the high exposure rate and the percentage of adult males seeking medical advice. A similar male predominance was reported by Gad et al.[16] *and* Mabrouk et al.[17]. These results are probably explained by the characteristics of the blood donor population who are presumably healthy adult males who seek medical assistance after being diagnosed in blood banks.

Furthermore, the median age of patients 49 years old ranging from 32 to 61 years old reflects that patients were infected during their active phases of life being subjected to the different risk factors of HCV infection. This result was also reported by Mabrouk et al., [17] who reported median age of 42 years old.

In our work, statistically significant difference was present in the child classification between the two groups as all group 1 are child A scoring 5 and group 2 were 34.8% of them child A scoring 6 and 65.2% of them were child B scoring 7. Also there was statistically significant difference in baseline laboratory data as regards serum albumin that was higher in group 1 than group 2 and INR that were higher in group 2**.** High Statistically significant difference was present in baseline platelet count that was higher in group 1 than group 2**.** This difference in baseline data is explained by the random selection of patients then classified according to the NCCVH [10] criteria.

In our work, statistically significant difference was present in baseline viral load that was higher in group 1 than group 2 which aggravates the evidence that the viral load did not influence the disease progression as all patients are cirrhotic and also did not affect the SVR rate ,this is in agreement with *Leroy et al.,*[18] who reported the same result by giving DAC/SOF/RBV for 12 week versus 16 week and SVR 12 did not decline in group with high viral load .

In this study, there was a statistically significant reduction in Hb level in group 2 at the end of treatment when compared with baseline level .The hemoglobin level <10 g/dL , (grade 3 severity) was not reported and no significant difference in group 1 , This was in agreement with *Kris et al.,*[19] who found that reductions in the hemoglobin level<9 g/dL occurred in 0% of all patients who received daclatasvir plus sofosbuvir.

In our work, there was a statistically significant increase in platelet count in group 1 and decreased in group 2 at the end of treatment when compared with baseline level. However, there was statistical significant difference when comparing the two groups with each other**.** This was in agreement with *Nelson et al., [20]* who found no reduction in platelet count in patients who received daclatasvir plus sofosbuvir. In all groups a

thrombocytopenia <50×10^3/mm^3 (grade 3 severity) were not reported and also in agreement with *Elsharkawy et al.,* [21] who found that no reduction in platelet count in patients who received sofosbuvir based regemen.

Also, there was a statistically significant difference at baseline WBCs count between groups 1, 2 which match with **N**CCVH Protocol [10]. Also there was a statistically significant difference in WBCs count in group 1 and 2 at the end of treatment towards increasing the count **.** This was in agreement with *Nelson et al*., [20] who reported that reductions in the neutrophil count <75 X 10^3/mm^3 occurr in 0% of all patients. In all groups a leucopenia <3×10^3/mm^3 (grade 3 severity) was not reported.

Also, as regard laboratory parameters among group 1 and group 2, there was statistical improvement of INR, decrease liver enzyme (ALT) and increase platelets count; a similar results was reported also by *Landis et al.,*[22] as sofosbuvir plus daclatasvir is tolerable in both cirrhotic and non cirrhotic patients **.**

In this work, there was a statistically significant improvement of INR in group 1 and no difference in group 2 that's in agreement with *Elsharkawy et al.,* [21] who found no elevation in INR levels in all groups treated with sofosbuvir based regiments.

Also, there is significant decrease in bilirubin level in group 1 and it increased significally in group 2 which match with Keating,[23] who found that the total bilirubin level >2.5mg occurred in 2% and 4-5% in those who received daclatasvir plus sofosbuvir and those who received daclatasvir plus sofosbuvir and ribavirin respectively .

In the present study, there was a statisticaly significant reduction in liver enzymes (ALT, AST) in group 1 and 2 at the end of treatment due to sustained virological response this agrees with Elsharkawyet al.[21] who found the decline in ALT and AST among all treatment sofosbuvir based regimens and also among different subgroups, namely cirrhotic and non- cirrhotic, which may indicate the significant role of DAAs in improving hepatic necro-inflammatory changes induced by viral infection. This constitutes one of the goals of therapy of chronic HCV as stated in the EASLE guideline[14]**.** However, *Landis et al.,* [22] founded that AST level of >5x the upper limit of normal (ULN) which occurred in (0.2% of daclatasvir plus sofosbuvir recipients and 1.5% of daclatasvir plus sofosbuvir and ribavirin recipients and ALT level of > 5 × ULN occurred in 0 and 1.0% respectively. This may be due to difference in selection of patients and difference in HCV genotyping.

Many clinical side effects were detected during treatment and most of adverse effects were of grade 1 severity. Adverse effects were mild without intervention or affection of Activities of Daily Living (ADL). No serious adverse events were detected and no patient stopped treatment due to adverse effects. The most commonly reported adverse events were fatigue, flu-like, rash and purities and headache. These finding are in agreement with EASL [14] which reported that the most common adverse reactions are fatigue, headache and nausea among daclatasvir plus sofosbuvir receipents.

As regard frequency, of adverse events were more frequent in group 2 patients than group 1 patients with statistically significant difference which may be explained by adding ribavirin to group 2. There was no adverse events after stoppage of treatment during patient follow up These results are agree with Hezode et al., [24] who found that headache affects (18.5 %) of daclatasvir plus sofosbuvir receipents versus (27.2 %) of daclatasvir plus sofosbuvir and ribavirin and fatigue affect (2.8 % and 15.3 %) respectively. Also,Paul et al.[25] reported that daclatasvir plus sofosbuvir (± ribavirin) was well tolerated in clinical trials. In patients receiving daclatasvir plus sofosbuvir in the ALLY-3 trial, and daclatasvir plus sofosbuvir plus ribavirin in the ALLY-3+ trial, no treatment-related deaths, discontinuations as a result of adverse events or treatment-related serious adverse events were reported. Across these trials, adverse events reported in more than 10 % of patients included headache, fatigue,nausea and insomnia.

As regard virological response for all treated patients ,there was negative PCR for HCV RNA at week 16(at the end of treatment) with 100% response in all treated patients which is still negative till 3 months after end of treatment except 5 patients in group 1 which make the SVR is 94.6% and 100% in group 1 and group 2 respectively. This is in agreement with Wyles et al.,[26]**,** who found that treatment naïve and treatment experienced patients with HCV genotype 3 or 4 infection who received daclatasvir plus sofosbuvir for 12 weeks, the SVR 12 rate was 100%.

This results was also matching with that reported by EASL [14] who found that combination of sofosbuvir and daclatasvir in patients genotype 1 without cirrhosis with 24 weeks of therapy, the SVR rates were 100%, without and with ribavirin, respectively) in treatment-naïve patients, and 100% and 95% without and with ribavirin, respectively, in patients who did not respond to the combination of pegylated IFN-a, ribavirin, and either telaprevir or boceprevir. With 12 weeks of therapy, SVR was achieved in 98% of treatment-naïve patients without ribavirin.

Also, Poordad et al.[27] found that chronic HCV genotype 3 or 4 infection receiving daclatasvir plus sofosbuvir and ribavirin for 12 weeks the SVR 12 rate ranged from 83 to 100%. In addition Leroy et al.,[18] **,** detected that chronic HCV genotype 3 receiving sofobuvir and daclatasvir plus ribavirin for 12 weeks, the SVR 12 weeks was 100% in patient with advanced fibrosis, SVR 12 was 86% in patient with cirrhosis and SVR 12 was 87% in patient with treatment experienced. This difference may be due to selection criteria as most

of our patients were child A (67.4%) and child B (32.6%) and difference in HCV genotyping.

CONCOLUSION

Daclatasvir plus sofosbuvir with or without ribavirin for 12 weeks is highly effective in treatment of naïve Egyptian patients with SVR 100% for (DAC/SOF/ RBV) and 94.6% for (DAC/SOF).

Based on liver biochemical profile analysis, we can conclude that Daclatasvir plus sofosbuvir is tolerable in patients with chronic HCV and improves hepatitis process caused by viral infection that evidenced by decreased liver enzymes level (AST,ALT).

Cirrhotic patients who added RBV still require careful observation during therapy being the more susceptible for treatment related complications as hyperbilirubinaemia and anemia.Adverse effects are mild ,tolerable ,without affection of activity of daily living (ADL) and no one in both groups stopped treatment . However, the heamatological adverse effects were highly significantly encountered in group 2 of patients who received (SOF /DAC/RBV).

Funding: None

Conflict of interest: The authors declare that they have no financial or non financial conflicts of interest related to the work done in the manuscript.

- Each author listed in the manuscript had seen and approved the submission of this version of the manuscript and takes full responsibility for it.
- This article had not been published anywhere and is not currently under consideration by another journal or a publisher.

Ethical approval: Approved by the ethical committee of Faculty of Medicine, Zagazig University.

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