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## RESEARCH ARTICLE

## Efficacy and Safety Of Sofosbuvir Plus Ribavirin In Chronic Hepatitis C Egyptian Patients with Child class A and B (comparative study).

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### Abstract

Many treatment regimens are available for treatment of chronic hepatitis c in different stages of the disease , include all oral direct acting antiviral agents (DAA) .

**Aim:-**The aim of our work was to compare the efficacy and safety of sofosbuvir and ribavirin in treatment patients with child class A and B in chronically infected HCV Egyptian patients.

**Patients and Methods:-** A total number of 132 chronic hepatitis C Egyptian patients were divided into two groups . Group 1 included 56 patients with child class A while group 2 included 76 patients with early child class B (score 7) . All patients were given sofosbuvir 400 mg once daily and weight based ribavirin (1200 mg daily if weight >75 kg or 1000 mg daily if weight ≤ 75kg ) for 6 months.

Inclusion and exclusion criteria were according to Egypt HCV Management Guidance at September , 2014 .

**Results:-** By the end of treatment , 93.75% of the patients had achieved SVR . SVR was 95 % in patients with child A and 92.6 % at child B group . The most common adverse effects were fatigue , anemia , jaundice, headache , insomnia , but 7.6 % of the patients had stopped the treatment due to severe complications.

**Conclusion:-** The findings from the present study suggest that 24 weeks of all-oral regimen of sofosbuvir plus ribavirin is an efficacious and well tolerated treatment in patients with chronic HCV infection and non inferior to currently available treatment options based on the proportion of patients who had achieved SVR.

Twenty four weeks of all-oral regimen of sofosbuvir plus ribavirin is an efficacious and well tolerated treatment in patients with chronic HCV infection and non inferior to currently available treatment options .

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### Introduction:-

It is estimated that up to 170-200 million people(3% of the world population) are chronically infected with HCV and about 350,000 person all over the world die from HCV associated chronic hepatic disorder each year but it is increasing for additional twenty years[1].

At 2008, Egypt was the commonest country having HCV cases in the world , so it is the biggest problem in it. About 14.7% of people in Egypt have HCV antibodies and 9.8% have an active infection[2].

Interferon (IFN)-based therapies represented the mainstay of treatment for HCV infection for years, but modifications of the treatment-regimens including pegylation of IFN and the addition of ribavirin (RBV) resulted in suboptimal improvement of sustained virologic response (SVR) and an unfavorable adverse effects profile. Based on the HCV

genotype (GT) and the treatment -experience, only 40% to 70% of patients achieved SVR[3]. But this helped to decrease prevalence in Egypt to 7% in 2015 [4].

The approval of the first-generation direct acting antiviral (DAA) agents, telaprevir (TLV) and boceprevir (BCV), in 2011 provided improvement in SVR for the targeted HCV GT1. Unfortunately, TLV and bcvtherapy was complicated by cumbersome schema of drug intake and the broad range of adverse events[5].

With the release of sofosbuvir in 2013 and 2014 in most Western countries, a new era in the treatment of chronic hepatitis C (CHC) began. An all-oral, IFN-free antiviral treatment for CHC with DAA agents became available for the first time. In addition to sofosbuvir, approvals of other second-generation DAA agents, which target different proteins of HCV have improved the efficacy of antiviral therapy with better tolerance[6].

SOF is pan-genotypic antiviral HCV-specific nucleotide inhibitor of viral NS5B polymerase that acts as chain terminator when incorporated as a substrate by RNA polymerase in the nascent HCV-RNA genome, leading to inhibition of viral replication which has a high barrier to resistance[7].

The aim of our study was to compare the efficacy and safety of sofosbuvir and ribavirin in treatment patients with child class A and B in chronically infected HCV Egyptian patients.

### **Patients and Methods:-**

This work had been carried out in Internal Medicine department, gastroenterology and hepatology unit, Zagazig University hospital, Egypt ; during the period from October 2014 to October 2015. A total number of 132 chronic hepatitis C Egyptian patients were divided into two groups . Group 1 included 56 patients with child class A while group 2 included 76 patients with early child class B (score 7) .

#### **Inclusion criteria:-**

According to Egypt HCV Management Guidance at September , 2014 [8].

Males and females more than 18 year, total bilirubin <5 mg/dl, albumin > 2.5 gm/ dl, platelet count >30000/ mm<sup>3</sup>, hemoglobin concentration ≥ 10 g/dl, serum creatinine < 2.5mg/dl or creatinine clearance >30% ,positive HCV RNA by PCR , glycosylated haemoglobin (hba1c) < 8 % in diabetic patients , normal alpha feto protein (AFP) and if more than 100 ng/ml , triphasic CT was done for exclusion of hepatocellular carcinoma (HCC) .

Female patient practicing adequate contraception during treatment period and at least 6 months after treatment stoppage.

The wife of male patient practicing adequate contraception .

#### **Exclusion criteria:-**

Presence or history of ascites and/or hepatic encephalopathy, patients with HCC except after successful radical curative intervention (3 months after resection or successful local ablation), presence of risky esophageal varices (sherry red spot or large esophageal or gastric varices) except after prophylactic management , other causes of liver diseases other than HCV induced hepatitis , pregnancy or breast feeding and creatinine > 2.5 mg/dl or creatinine clearance < 30%.

**Therapy:** all patients were given sofosbuvir 400mg once daily and ribavirin(RBV) 1200 mg daily if weight >75 kg or 1000 mg daily if weight ≤ 75kg.

**Duration:-** six months.

We start ribavirin dose by 800 mg daily and increase the dose 200 mg every one week according to hemoglobin level .

Written consents were taken from all patients included in the study. Results and possible adverse effects of the antiviral Regimen were explored to all patients received the therapy.

### **Methods:-**

All subjects of the study were subjected to the following:

- Thorough history and full physical examination, laboratory investigations as CBC, liver and kidney function tests, prothrombin time (PT), fasting blood sugar, HBA1c, AFP and HCV RNA by PCR.
- **Radiology :-**
  1. Pelvi abdominal Ultrasound.
  2. Triphasic CT if HCC is suspected by alph fetoprotein AFP>100ng/ml.
- Assesment of fibrosis by liver biopsy using Metavir score [9] or transient elastography (Fibroscan) [10].
- Assesment of decompensation by Child–Pugh’s classification [11].

#### Follow up by:-

- Quantitative PCR at weeks 4,12,24 and 36.
- ALT and AST at weeks 2,4,8,12,16,20 and 24.
- Total and indirect bilirubin at weeks 2,4,8,12,16,20 and 24.
- CBC at weeks 2,4,8,12,16, 20 and 24.
- Creatinine at weeks 4,8,12,16,20 and 24.

#### Criteria for dose reduction and modification according to hemoglobin level

Criteria for dose reduction and modification according to hemoglobin level		
Hemoglobin		
10 -11g/dl	<input type="checkbox"/> Sofosbuvir: No change <input type="checkbox"/> Ribavirin: ➤If no or minimal symptoms,then no dose modification. ➤If symptomatic,Decrease Ribavirin by 200mg	<b>Candidates for Erythropoietin</b> Rule out other causes of anemia. If anemia persists at 2 weeks after reducing Ribavirin and there is no hypertension, Then consider erythropoietin <b>Dosage:</b> erythropoeitinalfa 10,000 units subcutaneous /week
8.5 – 10g/dl	<input type="checkbox"/> Sofosbuvir: No change <input type="checkbox"/> Ribavirin:Decrease to 600mg/day(200mg by morning and 400mg by Evening).	
< 8.5 g/dl	<input type="checkbox"/> Sofosbuvir: No change <input type="checkbox"/> Ribavirin:Discontinue	
Consider treatment shift to future ribavirin free regimen when dose reduction of RBV and co-administration of erythropoietin for 2 consecutive weeks fail to elevate Hb level above 8.5 g/dl.		

[8].

#### Stoppage of treatment:

- Finishing treatment.
- Occurrence of severe side effects as anemia (Hb % <8.5g/dl) and jaundice (total bilirubin > 5mg/dl) or (indirect bilirubin > 2.5mg/dl) or liver decompensation as ascites, haematemesis or melena.

#### Statistical analysis:-

Knowledges were acquired, formulated and statistically explained by SPSS 19.0 for windows (SPSS Inc., Chicago, IL, USA) & Med Calc 13 for windows (Med Calc Software bvba, Ostend, Belgium).

**Results:-****Table 1:-** Comparison between studied groups as regard demographic data and history.

Demographic data & history	Group 1		Group 2		Test	P-value (Sig.)
	(N=56)		(N=76)			
	No.	%	No.	%		
Age (years)						
Mean $\pm$ SD	54.90 $\pm$ 8.42		57.33 $\pm$ 6.87		-1.720•	0.086
Median (Range)	56 (34 – 71)		58 (39 – 71)			(NS)
Sex						
Male	26	46%	35	46%	0.004‡	0.950
Female	30	54%	41	54%		(NS)
BMI (kg/m <sup>2</sup> )						
Mean $\pm$ SD	29.63 $\pm$ 3.92		29.94 $\pm$ 4.88		-0.400*	0.690
Median (Range)	29.75 (21.50 – 37.80)		29.50 (20.50 – 43)			(NS)
History						
Smoking	12	21%	8	10.5%	4.223‡	0.040
Previous treatment	15	26.7%	10	13%	4.123‡	0.042
HCC	5	8.9%	8	10.5%	0.091‡	0.762
						(NS)

• Mann Whitney U test.

\* Independent samples Student's t-test.

‡ Chi-square test. P&lt;0.05 is significant. Sig: Significance. NS: Non significant

**Table 2:-** Effect of treatment on total number of patients.

	<b>Total number (132)</b>
<b>ETR</b>	<b>112</b>
<b>SVR by PPA</b>	<b>105 ( 93.75%)</b>
<b>Treatment experienced</b>	<b>25 patients (19%)</b>
<b>ETR</b>	<b>21</b>
<b>SVR</b>	<b>20 (95.2%)</b>
<b>Treatment nieve</b>	<b>107 (81%)</b>
<b>ETR</b>	<b>92</b>
<b>SVR</b>	<b>85 (92.3%)</b>

**ETR** (End of treatment response)**PPA**(Per protocol analysis)

**Table 3:-** Comparison between both groups regarding sustained virological response (SVR) by PPA , relapse and effect of Previous treatment on efficacy.

	Group 1 N = 56	Group 2 N = 76	Test	P-value (Sig.)
Response	44/56	68/76	1.720‡	0.086 (NS)
SVR	42/44 (95%)	63/68 (92.6)	1.333‡	0.248 (NS)
Relapse	2/44 (4.5%)	5/68 (7.4%)	0.400‡	0.690(NS)
Non response	6/56 (10.7%)	4/76 (5.25%)	1.384‡	0.168(NS)
Discontinue*	6/56 (10.7%)	4/76 (5.25%)	1.368‡	0.242(NS)
<b>Previous treatment</b>	16/56 (28.6%)	9/76 (11.8%)	0.676‡	0.411(NS)
Response	12/16	9/9	1.572‡	0.210(NS)
SVR	11/12 (91.6)	9/9 (100%)	1.485‡	0.223(NS)
Relapsle	1/12 (8.3%)	0/9 (0%)	1.368‡	0.242(NS)
Non response	1/16 (6.25%)	0/9 (0%)	0.399‡	0.819(NS)
Discontinue	3/16 (18.75%)	0/9 (0%)	0.360‡	0.549(NS)
<b>Treatment naïve</b>	40/56 (71.4%)	67/76 (88.2%)	0.426‡	0.671(NS)
Responder	32/40	60/67 (89.6%)	0.065‡	0.799(NS)
SVR	31/32 (96.8%)	54/60 (90%)	0.028‡	0.867(NS)
Relapse	1/32 (3.1%)	6/60 (10%)	1.384‡	0.168(NS)
Non response	5/40 (12.5%)	3/67 (4.5%)	0.091‡	0.762(NS)
Discontinue	3/40 (7.5%)	4/67 (5.9%)	1.296‡	0.255(NS)

Discontinuation of treatment, due to anemia (Hb < 8.5 g/dl, after reduction of ribavirin dose and administration of erythropoietin 10000 u/w sc) in 2 patients (one in each group) and increase bilirubin >5 mg/dl in 8 patients (five in group 1 and 3 in group 2)

**Table 4:-** Comparison between Non responders and responders as regard:. Age, Smoking, PCR, DM, Bilirubin, Hb, , Fibrosis stage and Creatinine level.

	Non responder (N=10) No. (%)	Responder (N=112) No. (%)	Test‡	P-value (Sig.)
Age (years)	51-64	34 –71	1.720•	0.086 (NS)
Smoking	6 (60%)	18 (15%)	4.223‡	0.040 (S)
PCR (IU/ml)	1.778.990 784090	2997854 56400	1.368‡	0.242 (NS)
DM	50% (oral)	39 (34.8%) 26 ins,13 oral	1.485‡	0.223 (NS)
Bilirubin (mg/dl)	1.4 – 3.4	0.48 – 4	0.676*	0.411 (NS)
Hb (gm/dl)	8.7 – 14.3	9 – 15.3	1.232*	0.220 (NS)
Fibrosis	F3 – 4	F2 – 3	1.223•	0.269 (NS)
Creatinine (mg/dl)	0.8 – 1.67	0.6 – 1.1	0.483•	0.629 (NS)

**Table 5:-** Comparison between studied groups as regard adverse effects during treatment.

Adverse effects	Group 1		Group 2		Total	%
	(N=56)	%	(N=76)	%		
<b>Headache</b>	16	28.5 %	24	31.6 %	40	30%
<b>Fatigue</b>	27	48.2 %	40	52.6 %	67	50.7%
<b>Insomnia</b>	11	19.6 %	19	25%	30	22.7%
<b>GIT upsets</b>	9	16 %	17	22.4 %	26	19.7%
<b>*Anemia</b>	21	37.5 %	34	44.8 %	55	41.7
<b>*Hyperbilirubinemia</b>	16	28.6 %	30	39.5 %	46	34.8% %
<b>Discontinue Treatment</b>	6	10.7% %	4	5 %	10	7.6 %

**\*Anemia** : Reduction in hemoglobin level equal or less than 10 mg/dl at any week of treatment.

**\*Hyperbilirubinemia**: Bilirubin  $\geq$  2 mg/dl at any week of treatment.

**Table 6:-** Comparison between studied groups as regard complications after the end of treatment.

Complications	Group 1		Group 2		Test	P-value (Sig.)
	(N=56)		(N=76)			
	No=5	9%	No=6	8%		
Ascites	2	3.2%	3	3.75%	0.028‡	0.867 (NS)
Encephalopathy	0	0%	0	0%	---	---
Haematemesis	1	1.6%	1	1.25%	0.028‡	0.867 (NS)
Melena	2	3.2%	2	2.5%	0.133‡	0.715 (NS)

## Discussion:-

Achieving SVR is the target of treatment as viral load suppression not only reduce risk of HCV morbidity and mortality but also reduce the risk for future liver complications by 27 % ( e.g. Cirrhosis ,hepaocellular carcinoma , or liver related hospitalization) as well as reduce risk of death by 45 % ,relative to patients who did not achieve SVR [12]. Our study included 132 chronic HCV Egyptian patients treated with Sofosbuvir combination with ribavirin for 24 weeks . Fifty six patients had compensated cirrhosis (child A) and 76 patients were decompensated (child B) . By the end of treatment , 93.75% of the patients achieved SVR by per protocol analysis.

One hundred and seven patients were treatment naive with SVR 92.3 % while 25 patients were treatment experienced with SVR 95.2 % . Our results were similar to results of **Raune et al, [13]** . Their study on SOF plus ribavirin in genotype 4 treatment for 24 weeks, showed that SVR12 was achieved by 93% of patients ( treatment-naive and previously treated patients).

Patients with child A (56 patients ) had 95 % SVR while patients with child B (76 patients ) had 92.6 % SVR. These results matched results of **Smith et al, [14]**, who reported lower SVR in patients with liver cirrhosis than patients without liver cirrhosis, and higher SVR in child A > child B.

Our results were higher than results of **Doss et al, study[15]**. SVR rate was 90% (46/51) with 24 weeks of sofosbuvir and ribavirin therapy. Among all patients, 52% had received prior HCV treatment ( compared with 19% in our study ) and 17% had cirrhosis at baseline. Patients with cirrhosis at baseline had lower rates of SVR12 ( 78% ) than those without cirrhosis (93% ).

In our study, we had 107 treatment naive patients with 92.3% SVR while treatment experienced were 25 with 95% SVR . These result may be attributed to large number of naive patient (81%) compared to small number of treatment experienced (19%) .

The most common adverse events in our study were fatigue (50.7%), headache ( 30 % ), insomnia (22.7 ), GIT up sets in the form of nausea and abdominal pain (19.7% ) , anemia (41.7%) and hyperbilirubenemia (34.8%) .Ten patients (7.6%) had stopped treatment due to severe complications. Six patients in group 1 (10.7%) , most of them (5 patients) due to increased serum bilirubin more than 5mg/dl while one patient had stopped due to severe anemia. Four patients in group 2 (5%) had also stopped treatment ,three of them had stopped due to marked hyper bilirubenimia and the one was due to severe anemia.

These adverse events were nearly similar to results recorded by **Raune et al, [13] , Smith et al, [14] and Doss et al, [15]** ,but they reported no discontinuation of treatment . **Molina et al, [16]** reported six (2%) patients discontinued treatment because of sever adverse events.

There were significant increase in serum bilirubin in group 2 (30 patients ) more than group 1 (16 patients) . Eight patients had discontinued treatment due increased serum bilirubin more than 5 mg/dl during the treatment (five patients at group 1 and three patients at group 2).

There was significant reduction in hemoglobin level to less than 10 mg/dl in group 2 (34 patients) more than group 1 (21 patients). Reduction of ribavirin dose plus addition of erythropoietin at dose of 10,000 units subcutaneous /week succeeded to elevate hemoglobin level except in two patients who discontinued treatment .

These results comes in agreement with **Esmat et al.,[17]** whose study revealed decreased Hb in child B > child A . Smoking was the main significant factors in the group of non responders. It's known that smoking not only increase inflammation and fibrosis of the liver , as well as increase the risk of HCC , but also lower the response rate of CHC treatment **[18]**. Non responders had high fibrosis stage than responders but it was statistically insignificant.

No cases in our study had developed signs of decompensation as ascites, encephalopathy, haematemesis and melena during treatment , but during follow up after end of treatment ; two cases had developed ascites, one case had developed haematemesis and two cases had developed melena in group 1(8%). In group 2,three cases had developed ascites , 1 case had developed haematemesis and 2 cases had developed melena.This may necessitate long-term follow-up studies to confirm the durability of viral eradication in patients who achieve SVR.

### **Conclusion:-**

The findings from the present study suggest that 24 weeks of all-oral regimen of sofosbuvir plus ribavirin is an efficacious and well tolerated treatment in patients with chronic HCV infection and non inferior to currently available treatment options based on the proportion of patients who had achieved SVR.



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