Efficacy of Sofosbuvir and Ledipasvir in Comparison to Sofosbuvir and Daclatasvir in Management of Egyptian Chronic Hepatitis C Patients

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Background and study aim: In Egypt, the prevalence of hepatitis C virus (HCV) antibodies is the highest worldwide by 7.6%. Applying efficient treatment protocol on large scale could decrease HCV prevalence as well as disease burden.The aim of this study is to compare the efficacy of Sofosbuvir plus ledipasvir versus Sofosbuvir plus daclatasvir in management of chronic hepatitis C Egyptian patients with either easy to treat (naive patients with Child score A5)or difficult to treat (interferon experienced).

Patients and Methods: the study was performed on 200 chronic hepatitis C patients and they were classified into **Group I:** Included 100 patients fulfill criteria of [easy to treat] and were subdivided into two subgroups; **Group Ia:** 50 patients were treated with daily Sofosbuvir (400 mg) plus Daclatasvir (60 mg) for 12 weeks. **Group Ib:** 50 patients were treated with daily Sofosbuvir (400 mg) plus Ledipasvir (90 mg) for 12 weeks. **Group II:** Included 100 patients fulfill criteria of (difficult to treat) and were subdivided into two subgroups; **Group IIa:** 50 patients were treated with daily Sofosbuvir (400 mg) and Daclatasvir (60 mg) plus daily weight-based Ribavirin for 12 weeks; **Group IIb:** 50 patients were treated with daily Sofosbuvir (400 mg)) plus Ledipasvir (90 mg) plus daily weight-based Ribavirin for 12 weeks.

Results: **GIa:** 50 patients treated with Sof-Dac showed 100% cure (-ve PCR) at wk12 and wk 24. **GIb**: 50 patients treated with Sof-Led showed 98% cure (-ve PCR) at wk12 and wk 24. **GIIa:** 50 patients treated with Sof-Dac-Riba showed 100% cure (-ve PCR) at wk12 and 98% at wk 24. **GIIb:** 50 patients treated with Sof-Led-Riba showed 98% cure (-ve PCR) at wk12 and 96% at wk 24.The difference between treatment regimens (Sof + Dac or Sof + Lid with or without Riba), regarding the cure rate and adverse events in all the studied groups was not significant which indicates the safety and effectiveness of both medication regimens. The decrease in FIB4 calculation at week 24 was highly significant in comparison to the baseline in **GIa** (2.23 to 0.67) and **GIb** (2.1 to 1.12) (easy to treat, while the difference in FIB4 calculation was not statistically significant at week 24 in **GIIa** and **GIIb** (difficult to treat).

Conclusion: Both regimens are effective, well tolerated and showed excellent rate of sustained virological response (SVR).

INTRODUCTION

The WHO considered HCV as a global health issue, with approximately 3% of the global population (roughly 170-200 million people) infected with HCV. In the US, approximately 3 million people suffers from chronic HCV, some are still undiagnosed. The Egyptian situation is even worse. Egypt suffered the worst prevalence of hepatitis C in the world **[1]**.

In Egypt, in 2015, a demographic health survey (DHS) was done in Egypt revealing HCV anti-body prevalence nationwide of 6.7% and HCV RNA of 4.4% in age group (1–59) **[2]**.

FDA approved SOVALDI (sofosbuvir) at the end of 2013, for

the treatment of chronic hepatitis C (CHC) infection as a complementary antiviral treatment regimen in subjects with HCV genotype 1, 2, 3 or 4 infection, for HCV Genotype 4 infection as a triple therapy with Peg INF +RBV **[4]**.

Daclatasvir is an NS5A inhibitor with pan genotypic activity that is effective against the six major HCV genotypes with a dose of one tablet (60mg) every 24 hours. Daclatasvir with other combinations of suitable DAAs is prescribed to prevent emerging of resistance **[5]**.

AASLD and IDSA in 2016, have recommended ledipasvir to be first line treatment in combination with Sofosbuvir for the treatment of HCV genotypes 1a, 1b, 4, 5, and 6 **[6]**.

PATIENTS AND METHODS

This is a cross-sectional prospective study that was studied on 200 chronic hepatitis C Egyptian patients who were attending to National Hepatology & Tropical Medicine Research Institute, Cairo Egypt, to receive the anti-HCV oral therapy in concurrence with the Egyptian guidelines of treatment in the period between April 2016 to April 2018. Informed written consent was obtained for participation in the study for every patient. The protocol of the study and the informed consent forms were approved by the human subjects committee.

Inclusion criteria: Patients >18- <70 years old, positive serology for HCV Ab and HCV viremia, and compensated liver disease.

Exclusion criteria: Patients <18 or >70 years old, decompensated liver disease, pregnant or nursing females, coinfection with HBV, history of malignancy diagnosed or treated within 5 years, chronic use of systematically immunosuppressive agent, history of solid organ transplantation.

Patients were classified into: ***Group I Easy to treat:*** Easy to treat is defined as patient with the following: Treatment Naïve HCV patients, Serum Bilirubin < 1.2, Serum Albumin > 3.5, INR <1.2, Platelets > 150,000. It Included 100 patients fulfilling criteria of (easy to treat) and were subdivided into two subgroups; ***Group Ia:*** 50 patients received daily Sofosbuvir (400 mg) and Daclatasvir (60 mg) for 12 weeks. ***Group Ib:*** 50 patients received daily Sofosbuvir (400 mg) and Ledipasvir (90 mg) for 12 weeks. ***Group II Difficult to treat:*** Difficult to treat is defined as patient with one or more of the following: interferon experienced, Serum Bilirubin > 1.2, Serum Albumin < 3.5, INR >1.2, Platelets < 150,000 ***:*** It Included 100 patients fulfill criteria of **(**difficult to treat**)** and will be subdivided into two subgroups; ***Group IIa:*** 50 patients received daily Sofosbuvir (400 mg) and Daclatasvir (60 mg) and daily weight-based Ribavirin (RBV) (1000 mg [<75 kg] to 1200 mg [≥75kg]) for 12 weeks. ***Group IIb:*** 50 patients received daily Sofosbuvir (400 mg) and Ledipasvir (90 mg) and daily weight-based Ribavirin (RBV) for 12 weeks as advised by National committee for control of viral hepatitis. NCCVH.[7]

Patients were subjected to the following;

Prior to treatment: 1- Full history taking, 2- Through Clinical examination 3- Abdominal ultrasonography: It was done using Toshiba SSA-340A machine with a 3.5MHZ curved convex probe. 4- Laboratory part of the work including:

- Biochemical tests: a- Complete blood picture: Which were done on Sysmex (Germany). **b- Liver and kidney function tests**: Which were done on Cobas c311 auto analyzer (Germany) using Roch reagent kits, prothrombin time, concentration and INR, fasting blood sugar, HBA1c for diabetics, Alfa feto protein, HCV PCR Quantitative, HBsAg.

-Fib 4 for assessment of fibrosis: FIB-4 score was used as a non-invasive routine biochemical method to assess fibrosis stage. It was calculated for patients before and after the end treatment.

FIB-4	**Age (years) × AST [U/l] / (platelets [10^9/L] × (ALT [U/L])$^{1/2}$)**

-Monitoring of treatment safety: For all patients: liver biochemical profile, complete blood count and creatinine were tested every visit (1 month). Patients were asked about the commonly reported adverse events as headache, nausea, insomnia, pruritus, fatigue, rash, photosensitivity.

-Monitoring of treatment efficacy at the end: All patients were followed up by CBC, liver functions, kidney functions at weeks 4, 8, end of treatment and week 24. Quantitative PCR for HCV was done at weeks 0, 12, 24 (SVR 12, 24) Virologic response was considered when HCV RNA is less than the lower limit of detection at end of treatment and post treatment at week 24

-Statistical Analysis: Analysis of data was performed using SPSS v. 16. (Statistical Package for Scientific Studies) for Windows.

RESULTS

Table (1): Comparison between laboratory data pretreatment and post treatment in Group Ia group.

		Group Ia		Mean difference ± SE	Test value	P-value
		Pre	Post			
ALT unit/dl	**Mean ± SD**	59.23 ± 37.45	42.56 ± 20.84	-16.67 ± 5.13	3.251	0.002
	Range	12.38 – 236.67	21 – 95.26			
AST unit/dl	**Mean ± SD**	66.62 ± 54.41	49.95 ± 22.43	-16.66 ± 7.59	3.701	0.001
	Range	17.3 – 346.32	20 – 90			
Albumin gm/dl	**Mean ± SD**	4.14 ± 0.36	3.91 ± 0.31	-0.23 ± 0.06	2.194	0.033
	Range	3.5 – 4.9	3.5 – 4.3			
Total BILIRUBIN mg/dL	**Mean ± SD**	0.92 ± 0.32	0.73 + 0.21	0.18 ± 0.05	3.524	0.001
	Range	0.27 – 1.41	0.3 + 1.1			
PC %	**Mean ± SD**	90.72 ± 8.19	93.76 ± 7.38	3.04 ± 1.49	-2.038	0.047
	Range	78 – 100	82 – 100			
INR	**Mean ± SD**	1.03 ± 0.05	1.10 ± 0.18	0.1 ± 0.026	2.910	0.05
	Range	1 – 1.1	1 – 1.2			
AFP IU/L	**Mean ± SD**	10.82 ± 10.78	10.28 ± 1.71	0.02 ± 1.34	-0.016	0.987
	Range	3 – 57	8 – 20			

This table shows that, there was a statistically significant improvement in all liver functions studied, post treatment in comparison to pretreatment in GIa, while AFP show insignificant changes.

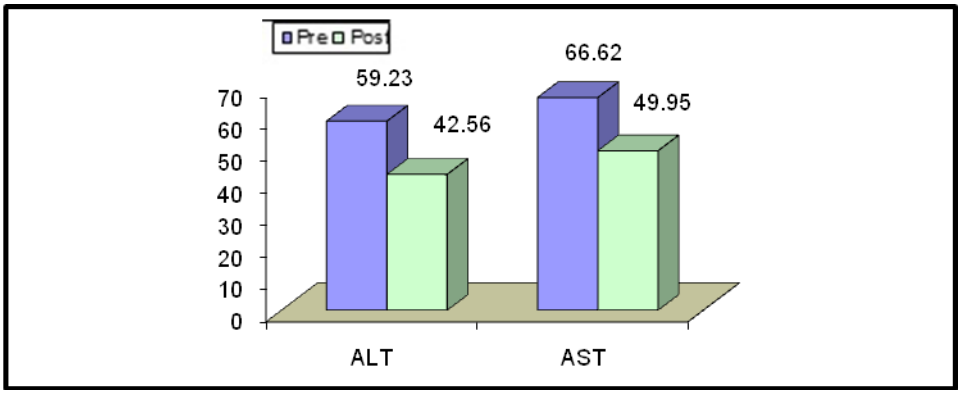

Fig. (1): Shows ALT, AST in Group Ia pre and post treatment

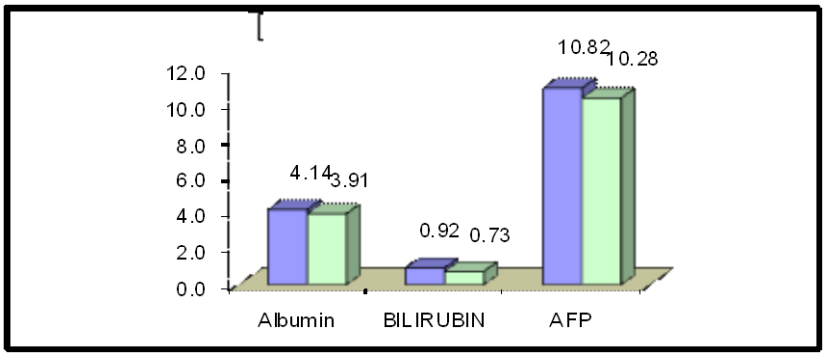

Fig. (2): shows Albumin, bilirubin, AFP in Group Ia pre and post treatment.

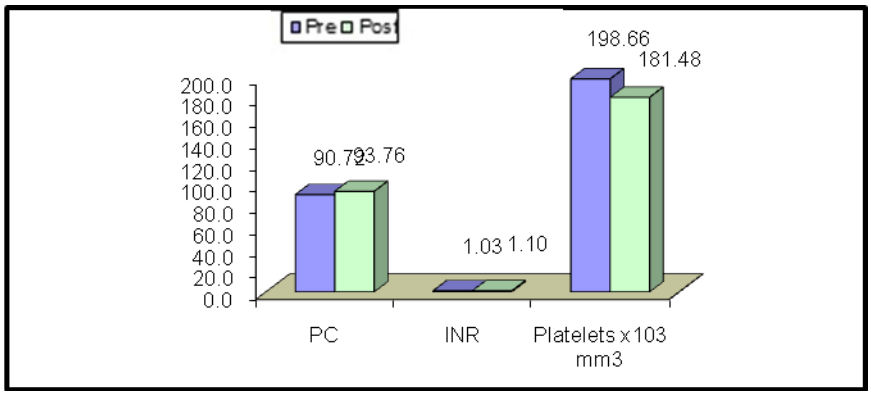

Fig. (3): Shows platelets, Prothrombin concentration, INR in GroupIa pre and post treatment.

Table (2): Comparison between the Complete blood Count data pretreatment and post treatment in Group Ia group

		Group Ia		Mean difference ± SE	Test value	P-value
		Pre	Post			
WBC x 10^3mm^3	**Mean ± SD**	6.89 ± 2.06	5.90 ± 1.92	-0.99 ± 0.43	2.278	0.027
	Range	3.4 – 14.1	2.6 – 10.4			
HbG/dL	**Mean ± SD**	14.25 ± 1.36	13.10 ± 1.62	-1.15 ± 0.29	3.951	0.020
	Range	11.7 – 17.2	10 – 16.6			
Platelets x 10^3 mm^3	**Mean ± SD**	198.66 ± 40.96	181.48 ± 31.93	-17.18 ± 8.08	2.127	0.038
	Range	150 – 327	160 – 320			

This table shows CBC results there was significant difference between pretreatment and post treatment in GIa

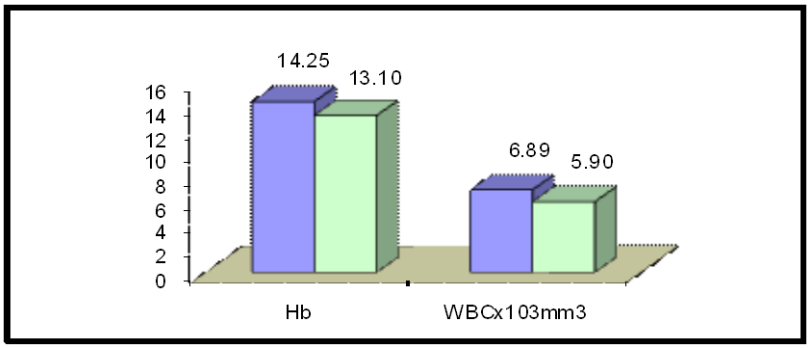

Fig. (4): Shows hemoglobin and white blood cells in Group Ia pre and post treatment.

Table (3): Comparison between laboratory data pretreatment and post treatment in Group I b group

	GIb	Pre	Post	Mean difference ± SE	t-test	p-value
ALT	**Mean ± SD**	59.40 ± 33.40	46.28 ± 25.17	-13.12 ± 6.13	2.139	0.037
	Range	10 – 154.44	18 – 106.86			
AST	**Mean ± SD**	55.16 ± 26.76	54.23 ± 19.29	-0.94 ± 4.46	0.210	0.834
	Range	7.57 – 140	30 – 89			
Albumin g/dL	**Mean ± SD**	3.79 ± 0.23	4.13 + 0.40	-0.34 ± 0.06	5.312	0.000
	Range	3.5 – 4.3	3.5 – 4.9			
Total BILIRUBIN mg/dL	**Mean ± SD**	0.91 ± 0.30	0.72 ± 0.26	0.18 ± 0.06	-3.146	0.003
	Range	0.27 – 1.2	0.3 - 1.1			
PC	**Mean ± SD**	91.00 ± 7.46	91.36 ± 4.04	0.36 ± 1.27	-0.283	0.778
	Range	82 – 100	88 – 100			
INR	**Mean±SD**	1.03 ± 0.05	1.18 ± 0.19	0.15 ± 0.03	-5.268	0.000
	Range	1 – 1.1	1 – 1.2			
AFP	Mean±SD	10.26 ± 13.12	10.53 ± 3.13	0.02 ± 2.14	0.010	0.992
	Range	5 – 77	6 – 30			

This is table shows there was significant decrease in, bilirubin, ALT, while there was significant increase in s. Albumin and INR post treatment in comparison to pretreatment in GIb.

Table (4): Comparison between Complete Blood Count pretreatment and post treatment in Group Ib

GIb	Group 1	Pre	Post	Mean difference ± SE	t-test	p-value
WBCx10^3/mm^3	**Mean ± SD**	6.32 ± 1.79	5.06 ± 1.86	-1.26 ± 0.38	3.282	0.002
	Range	3.6 – 11.4	2.5 – 10.4			
Hb/GL	**Mean ± SD**	13.97 ± 1.54	13.33 ± 1.44	-0.64 ± 0.30	2.100	0.041
	Range	10 – 16.6	10.4 – 16			
Platelets x10^3 /mm^3	**Mean ± SD**	196.76 ± 44.47	183.26 ± 34.93	-13.5 ± 7.99	1.689	0.097
	Range	165 – 341	165 – 338			

This table shows CBC results as there was no significant difference in the platelet count between pretreatment and post treatment in GIb except WBCs there was a statistically significant decrease.

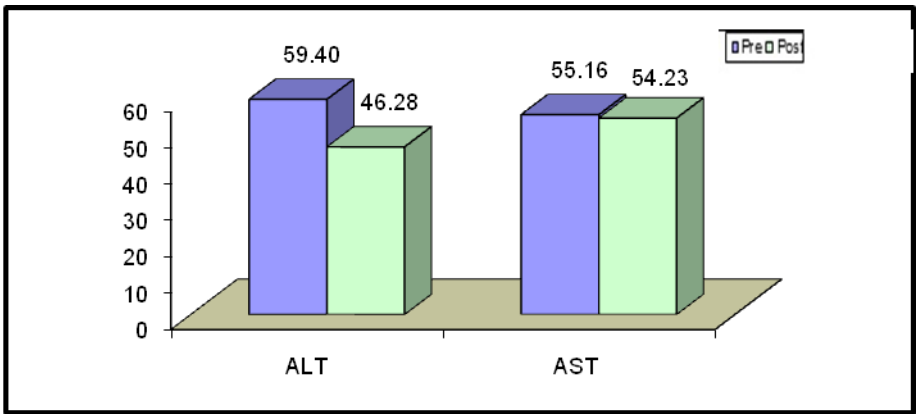

Fig. (5): Comparison between ALT, AST pretreatment and post treatment in Group Ib

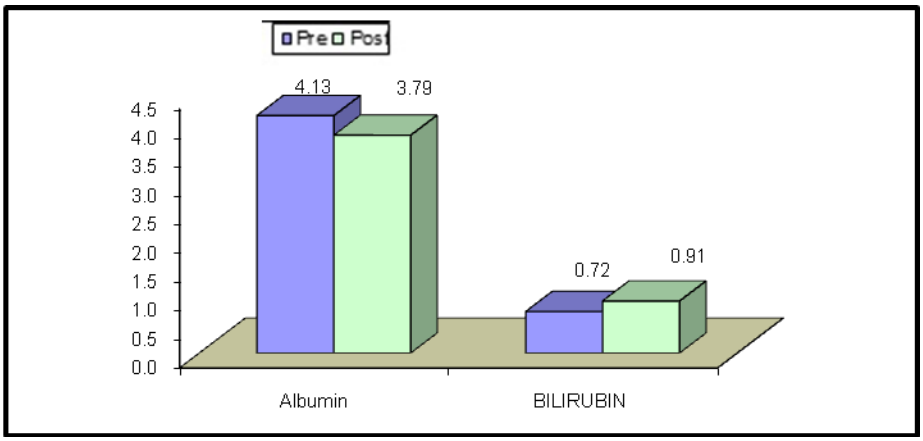

Fig.(6): Comparison between Albumin and bilirubin pretreatment and post treatment in Group Ib

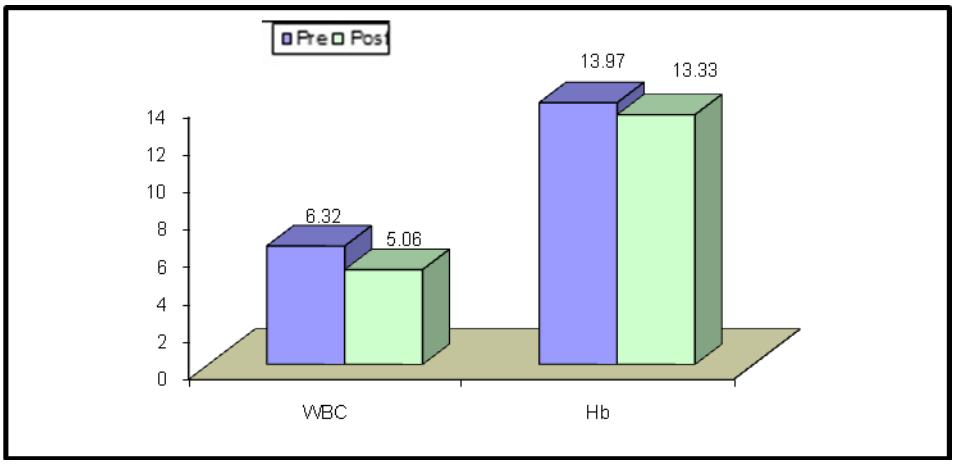

Fig. (7): Comparison between white blood cells and hemoglobin pretreatment and post treatment in Group Ib

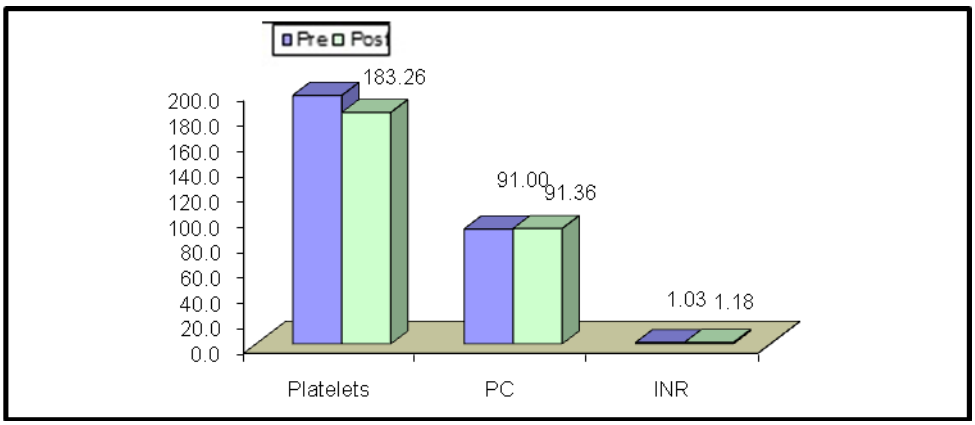

Fig. (8): Comparison between platelets, Prothrombin concentration, INR pretreatment and post treatment in Group Ib

Table (5): Comparison between laboratory data pretreatment and post treatment in Group IIa

		Group IIa		Mean diff ± SE	Test value	P-value
		Pre	Post			
ALT	**Mean ± SD**	69.46 ± 47.28	43.07 ± 18.51	-26.39 ± 7.35	3.591	0.001
	Range	10 – 270	9 – 87			
AST	**Mean ± SD**	87.89 ± 54.18	54.94 ± 20.47	-32.95 ± 7.74	4.259	0.000
	Range	10 – 282	22 – 93			
Albumin g/dL	**Mean ± SD**	3.52 ± 0.57	3.10 ± 0.29	-0.42 ± 0.08	5.144	0.000
	Range	2.8 – 4.9	2.8 – 4			
Total BILIRUBIN mg/dL	**Mean ± SD**	1.21 ± 0.60	1.18 ± 0.55	-0.03 ± 0.09	0.343	0.733
	Range	0.3 – 2.5	0.5 – 4			
PC	**Mean ± SD**	76.74 ± 12.26	90.34 ± 11.20	13.60 ± 2.44	-5.572	0.000
	Range	62 – 100	65 – 100			
INR	**Mean ± SD**	1.25 ± 0.18	1.05 ± 0.07	-0.21 ± 0.03	7.271	0.000
	Range	1 – 1.6	1 – 1.32			
AFP IUL	**Mean ± SD**	18.74 ± 18.42	12.02 ± 9.89	-6.72 ± 3.03	2.221	0.031
	Range	3 – 82	10 – 60			

This is table shows there was significant decrease in AST, ALT, INR and AFP, while there was significant increase in PC post treatment in comparison to pretreatment in GIIa & insignificant changes in bilirubin.

Table (6): Comparison between Complete Blood Count pretreatment and post treatment in Group IIa

		Group IIa		Mean diff ± SE	Test value	P-value
		Pre	Post			
WBC x 10^3 mm^3	**Mean ± SD**	5.04 ± 2.02	6.53 ± 8.83	1.49 ± 1.30	-1.143	0.259
	Range	2.6 – 14.1	3.4 – 67			
Hb G/L	**Mean ± SD**	13.27 ± 1.72	13.53 ± 1.40	0.26 ± 0.27	-0.960	0.342
	Range	10.4 – 16.6	10 – 15			
Platelets x10^3 mm^3	**Mean ± SD**	95.46 ± 32.80	161.64 ± 29.98	66.18 ± 6.51	-10.172	0.000
	Range	65 – 248	70 – 230			

This table shows there was highly significant increase in platelet count, post treatment in comparison to pre treatment, while there was no significant differences in WBCs and hemoglobin in GIIa

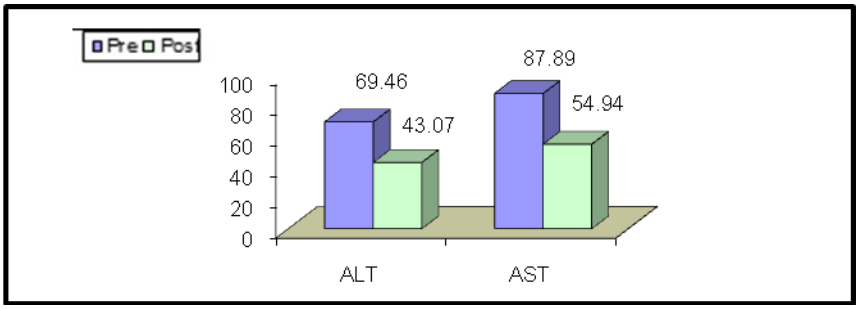

Fig. (9): Comparison between ALT, AST pretreatment and post treatment in Group IIa

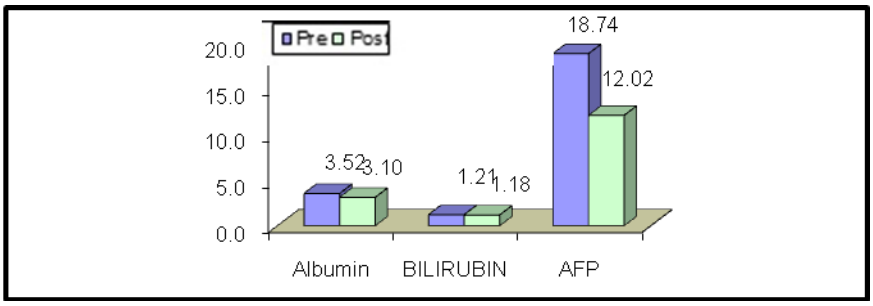

Fig. (90): Comparison between Albumin, bilirubin, AFP pretreatment and post treatment in Group IIa

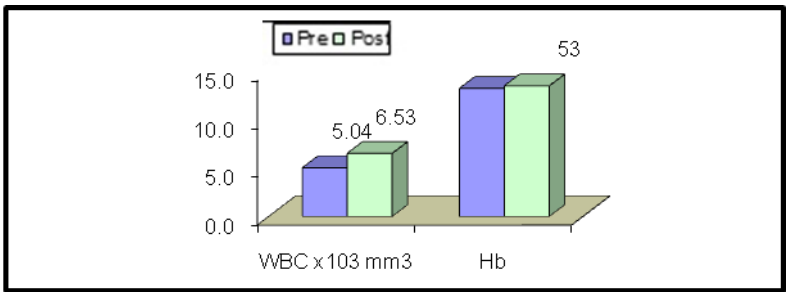

Fig. (101): Comparison between WBC and hemoglobin pre and post treatment in Group IIa.

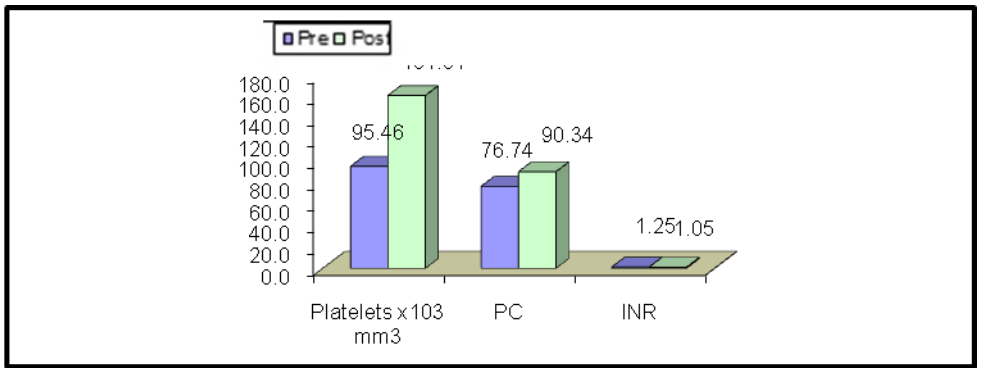

Fig. (112): Comparison between platelets, PC, INR pre and post treatment in Group IIa

Table (7): Comparison between laboratory data pretreatment and post treatment in Group IIb

		Group IIb		Mean diff ± SE	Test value	P-value
		Pre	Post			
ALT	**Mean ± SD**	55.17 ± 33.05	43.37 ± 20.64	-11.80 ± 4.99	2.362	0.022
	Range	13.6 – 160	7 – 98			
AST	**Mean ± SD**	71.40 ± 35.82	45.45 ± 21.76	-25.95 ± 5.83	4.454	0.000
	Range	5 – 169	15 – 75			
Albumin g/dL	**Mean ± SD**	3.66 ± 0.60	3.09 ± 0.50	-0.57 ± 0.12	4.822	0.000
	Range	2.8 – 4.9	1 – 4.6			
Total BILIRUBIN mg/dL	**Mean ± SD**	1.20 ± 0.52	1.06 ± 0.18	-0.14 ± 0.08	1.789	0.080
	Range	0.4 – 2.4	0.7 – 1.6			
PC	**Mean ± SD**	80.90 ± 13.32	90.82 ± 11.02	9.92 ± 2.32	-4.280	0.000
	Range	60 – 100	69 – 100			
INR	**Mean ± SD**	1.21 ± 0.20	1.04 ± 0.08	-0.17 ± 0.03	5.628	0.000
	Range	1 – 1.7	1 – 1.36			
AFP IUL	**Mean ± SD**	15.78 ± 14.86	13.90 ± 12.16	-1.88 ± 2.38	0.789	0.434
	Range	7 – 75	9 – 50			

This table shows there was significant decrease in ALT, AST, s. bilirubin, s. albumin and INR, while there was significant increase in PC post treatment in comparison to pretreatment in GIIb.

Table (8): Comparison between the CBC pre and post treatment in Group IIb

		Group IIb		Mean diff ± SE	Test value	P-value
		Pre	Post			
WBC x10^3 mm^3	**Mean ± SD**	4.82 ± 1.91	5.31 ± 1.21	0.49 ± 0.30	-1.614	0.113
	Range	2.4 – 11.2	3.4 – 8			
Hb/GL	**Mean ± SD**	13.41 ± 1.28	13.64 ± 1.44	0.23 ± 0.27	-0.848	0.401
	Range	10.6 – 16.8	10 – 15			
Platelets x10^3 mm^3	**Mean ± SD**	112.48 ± 49.12	164.34 ± 25.60	51.86 ± 7.59	-6.829	0.000
	Range	74 – 260	80 – 212			

This table shows there was significant increase in platelet count post treatment in comparison to pretreatment in GIIb

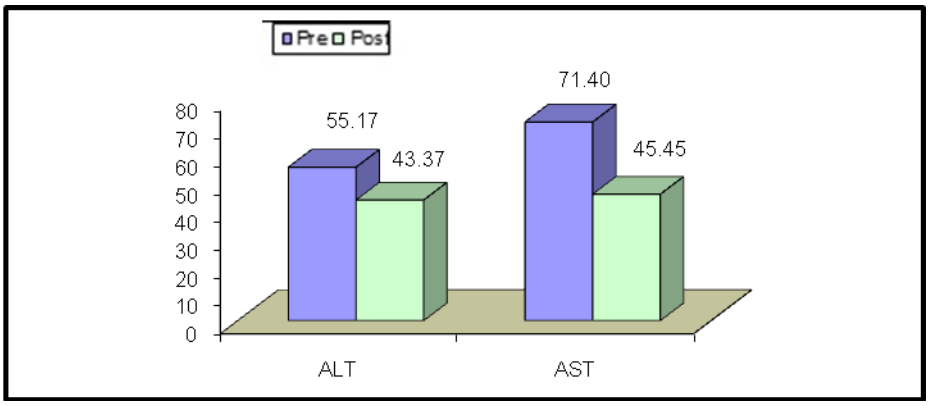

Fig. (13): Comparison between ALT, AST pre and post treatment in Group II b

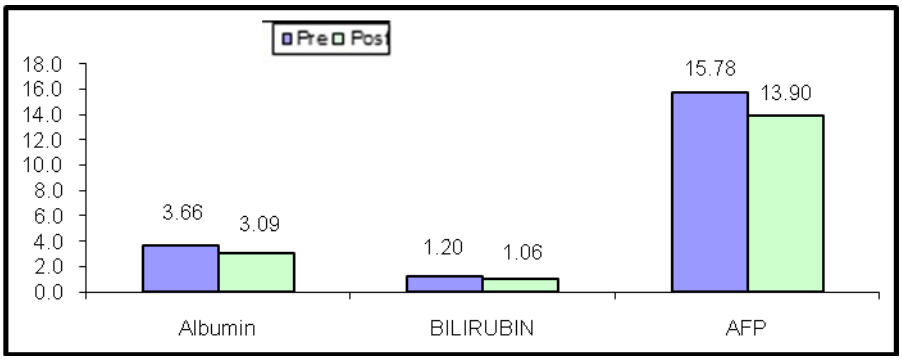

Fig. (124): Comparison between Albumin, bilirubin, AFP pre and post treatment in Group II b

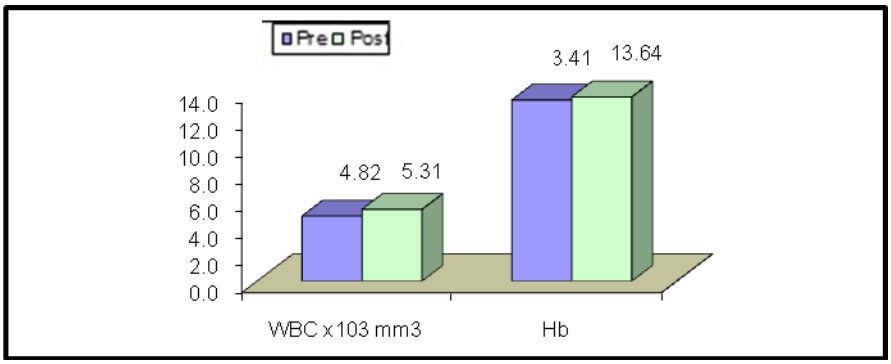

Fig. (135): Comparison between WBC and hemoglobin pre and post treatment in Group II

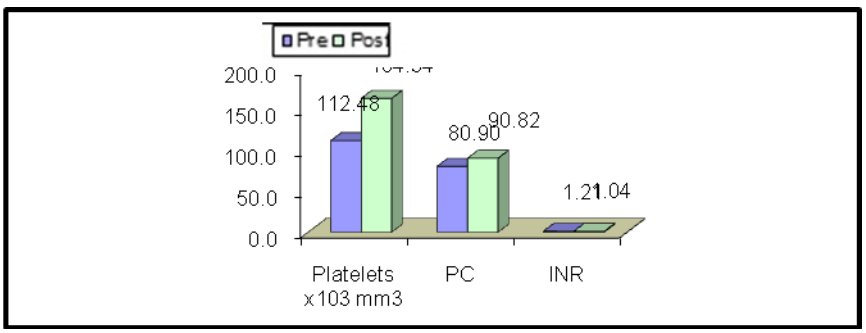

Fig. (146): Comparison between platelets, PC, INR pre and post treatment in Group II b

Table (9): FIB4 calculation in Group I pre and post treatment

Fib4 Calculation	Group Ia		P-value	Group Ib		P-value
	Baseline	24 w		Baseline	24 w	
Mean ± SD	2.23 ± 1.12	0.67 ± 0.31	<0.001	2.13 ± 1.11	1.12 ± 0.59	<0.001
Range	0.33 – 5.12	0.14 – 1.77		0.38 – 4.73	0.2 – 2.64	

There was highly significant decrease in FIB4 calculation at week 24 in comparison to the baseline in GIa & GIb.

Table (50): FIB4 calculation in Group II pre and post treatment

Fib4 Calculation	Group IIa		P-value	Group IIb		P-value
	Baseline	24 w		Baseline	24 w	
Mean ± SD	6.83 ± 4.55	4.81 ± 3.30	0.063	6.12 ± 4.02	5.83 ± 3.45	0.699
range	0.58 – 25.51	0.38 – 21.97		0.22 – 19.26	0.17 – 18.43	

There was no statistically significant decrease in FIB4 calculation at week 24 in comparison to the baseline in GIIa & GIIb

Table (61): Shows comparison between the PCR results in the studied groups at week 12 and 24.

		Group I				P-value*	Group II				P-value*
		GIa		GIb			GIIa		GIIb		
		No.	%	No.	%		No.	%	No.	%	
HCVRNAW12	Negative	50	100 %	49	98%	0.315	50	100%	49	98.0%	0.315
	Positive	0	0.0%	1	2.0%		0	0.0%	1	2.0%	
_ HCVRNAW24	Negative	50	100.0%	49	98.0%	0.315	49	98.0%	48	96.0%	0.558
	Positive	0	0.0%	1	2.0%		1	2.0%	2	4.0%	

This table shows the results of quantitative PCR at wk 12 and wk 24

- In GIa : showed 100% cure (-ve PCR) at wk12 and wk 24, while in GIb : showed 98% cure (-ve PCR) at wk12 and wk 24. In GIIa : showed 100% cure (-ve PCR) at wk12 and 98% at wk 24, while in GIIb : showed 98% cure (-ve PCR) at wk12 and 96 at wk 24. There was no statistical difference in the cure rate in different groups of the study.

DISCUSSION

As regard liver functions pre and post treatment, there was significant decrease in ALT, AST and s. bilirubin post treatment in comparison to pretreatment in GIa, while there was significant decrease in ALT and s. albumin and significant increase in s. bilirubin and INR post-treatment in comparison to pretreatment in GIb.

Also there was significant decrease in ALT, AST and INR, while there was significant increase in PC post-treatment in comparison to pre-treatment in GIIa, while there was significant decrease in ALT, AST, s. bilirubin, s. albumin and INR, and there was significant increase in PC post-treatment in comparison to pre-treatment in GIIb. So we concluded that there was no significant deference between two regimens.

As regard comparison of CBC results post treatment and pretreatment there was no significant difference between pre-treatment and post-treatment in GIa and GIb, while there was highly significant increase in platelet count, post treatment in comparison to pre-treatment in GIIa and GIIb indicate that there was no significant deference between two regimens.

As regard FIB4 calculation, there was highly significant decrease in FIB4 at week 24 in comparison to the baseline in GIa (2.23 to 0.67) and GIb (2.1 to 1.12) (easy to treat) , while there was no statistically significant deference in FIB4 calculation at week 24 in GIIa and GIIb (difficult to treat). This can be explained by the fact that in advanced liver disease there is little improvement of liver condition after DAAs therapy in 24 wks period.

This was in agreement with Wong et al.**[8]** whose study showed Among 2691 patients, all

markers of disease severity demonstrated sustained improvements from pre-treatment to 4 years post-treatment.

As regard the virological response by quantitative PCR in the studied groups In GIa: showed 100% cure (-ve PCR) at wk12 and wk 24, while in GIb: showed 98% cure (-ve PCR) at wk12 and wk 24.

Also In GIIa: showed 100% cure (-ve PCR) at wk12 and 98% at wk 24, while in GIIb showed 98% cure (-ve PCR) at wk12 and 96 at wk 24.

This goes in agreement with Shiha et al. **[9]** who found that SVR is 96% after treatment of 177 patients with SOF+DAC for 3 months in comparison to our study SVR is 100%.

Also, this was in agreement with Ahmed et al. **[10]** who found that SVR was 98% after treatment of 43 patients with SOF+LED for 3 months. In Fontaine et al. **[11]**, SVR is 100% in comparison to our study SVR is 98%. We can notice that SVR in our study is less than Fontaine et al. trial **[11]**, and it could be due to, the large number in our study (50 patients in comparison to 15 patients in Fontaine et al. **[11]**, trial, and our study included Naïve patients group, while Fontaine et al. **[11]**, trial included only experienced patients.

In conclusion: Both regimens are effective, well tolerated and associated with high rate of sustained virological response (SVR).

Ethical considrations: This paper was conducted after IRB approval from Al -Azhar university, informed concent was taken from each patient.

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