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Pegylated Interferon, Ribavirin, and Sofosbuvir Combination Versus Pegylated Interferon, Ribavirin in The Management of Chronic Hepatitis C Egyptian Patients

Abdel-Hameed I. Ebid[1]*, Mohammed A. Mobarez[1], Mohamed A. Mahmoud[1], Ramadan A. Ramadan[2]

[1]*Department of Pharmacy Practice, Faculty of Pharmacy, Helwan University, Cairo, Egypt.*
[2]*Internal Medicine, Hepatology Department, Ahmed Maher Teaching Hospital, Cairo, Egypt.*

*__Corresponding author__: *Abdel-Hameed I. Ebid; Department of Pharmacy Practice, Faculty of Pharmacy, Helwan University. Cairo, Egypt, 11795. Tel.: +202-01001423032; fax: +202-2554-1601*
E-mail address: nouran100@yahoo.co.uk

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ABSTRACT

Objective: The aim of this study is to comprehensively evaluate the safety and efficacy of the 20-kDa linear (Pegylated Interferon) PEGIFN alpha-2a and Ribavirin combination versus Sofosbuvir, 20-kDa linear PEGIFN alpha-2a and Ribavirin combination in treatment of chronic hepatitis C (CHC) Egyptian patients as well as studying variables that affect the response to this treatment. **Methods:** A total of 202 adult Egyptian patients divided into 2 groups; IR group composed of 97 patients enrolled to receive PEG-IFN and RBV combination treatment, and IRS group composed of 105 patients enrolled to receive PEG-IFN, RBV, and sofosbuvir combination. **Results:** In IR group 62 (63.92%) had end of treatment response (ETR), of the 62 patients with ETR, 11(11.34%) had a relapse while 51 (52.58%) patients achieved sustained virological response (SVR). In IRS group six (5.72%) patients were non-responders, where as 99 (94.28%) patients attained ETR of whom 29 (27.62%) had a relapse while 70 (66.67%) patients achieved SVR. **Conclusion:** This new combination containing sofosbuvir is still ineffective enough so that more researches and treatment combination needed to combat hepatitis C epidemic in Egypt at reasonable cost.

Key Words: *HCV, Interferon, Ribavirin, Sofosbuvir, SVR.*

INTRODUCTION

Hepatitis C virus (HCV) infection is the principal cause of chronic liver disease, Hepatocellular carcinoma (HCC) and the leading indication for liver transplantation.[1] Nearly 150 million people worldwide are currently infected with the HCV[2] and approximately 3.2 to 5.2 million of these individuals are in the United States[3,4]. In Egypt, the situation is quite worse. The national prevalence rate of HCV antibody positivity estimated at 14.7% of the country's population[5,6], with an estimated 91% of infections are caused by genotype 4.[7-9] So, Egypt has the highest HCV seroprevalence in the world.[10-12] Today, HCV infection and its complications are among the leading public health challenges in Egypt.[13] Previously, the most effective therapy available for chronic hepatitis C (CHC) was subcutaneous injection of interferon (IFN) alpha combined with oral ribavirin (RBV).[14,15] Both IFN alpha-2a and IFN alpha-2b have a serum half-life of <12 hours. Thus, thrice-weekly subcutaneous injections are required to maintain effective drug concentrations for the treatment of CHC.[16,17] However, a majority of patients fail to clear the virus i.e., achieve a sustained virological response (SVR) with this treatment.[18,19] Conjugation of polyethylene glycol (PEG) to several biologic response-modifying proteins has been shown to increase the proteins' serum half-life, reduce their sensitivity to proteolysis, and reduce antigenicity.[20,21] Co-administration of PEGIFN alpha-2a and RBV has been shown to further improve the anti-HCV activity of IFN.[22] Sofosbuvir is a uridine nucleotide analog, with specific inhibition of HCV NS5B RNA-dependent RNA polymerase (RdRp) activity. Sofosbuvir remains largely intact in transit through the gastrointestinal system and is efficiently taken up by hepatocytes.[23] Through sequential

hydrolysis by hepatic serine protease cathepsin A (CatA) and serine esterase carboxyl esterase 1 (CES1), the active form (GS-566500) is created. This compound is further hydrolyzed by histidine followed by two additional phosphorylations through the pyrimidine biosynthesis pathway to create the pharmacologically active nucleoside analog triphosphate (GS-461203).[24]

The *NEUTRINO* study[25] was a single-group, open label study of treatment-naive patients with hepatitis C genotype 1, 4, 5, and 6, treated with SOF plus PEG and RBV for 12 weeks. The study population of 327 included 17% patients of African descent and 17% with cirrhosis. Ninety percent of patients in this analysis attained sustained viral response.

MATERIALS AND METHODS

Patient Selection

Patients were screened and entered the study if they: were aged 18-65 years old, had at least one elevated serum alanine aminotransferase (ALT) level more than twice the upper limit of normal during the 6 months before treatment, had positive serum anti-HCV antibodies, had a detectable HCV-RNA on testing with polymerase chain reaction (PCR), and agreed to sign an informed consent to participate in the study.

Patients were excluded from the study if they don't meet the above mentioned inclusion criteria, had other causes of chronic liver disease (hepatitis B infection, autoimmune hepatitis, metabolic liver disease such as hemochromatosis or chronic alcoholism), were co-infected with human immunodeficiency virus (HIV), were pregnant or breast feeding females, had ischemic heart disease (IHD), had severe neurologic or psychological conditions, had hematologic conditions such as white blood cell (WBC) count $<3.5\times10^6$ /mm^3, absolute neutrophilic count (ANC) <1500 /mm^3, hemoglobin (Hg) <12 gm/dl, or platelet (PLT) count <100,000 /mm^3, or had autoimmune disease, hemolytic anemia, or poorly controlled diabetes mellitus.

Table 1. Demographic characteristics of studied patients

Characteristic		Mean ± SD		Range		*P*-value	Sig.
		IR Group	IRS Group	IR Group	IRS Group		
Number of patient		97	105				
Gender (n/%)	Male	79/81.45	62/59.04			0.001	Sig.
	Female	18/18.55	43/40.95				
Age (years)		48.51 ± 8.01	49 ± 7.26	32 – 64	35 – 62	0.646	Ns.
Body Weight (kg)		69.4 ± 12.23	73.97 ± 11.39	44 – 118	40 – 100	0.074	Ns.

SD: standard deviation; Sig: significant; Ns: non significant

Study design

A cohort study-comparing safety and efficacy parameters of patients at Ahmed Maher Teaching Hospital previously untreated CHC enrolled to receive linear pegylated interferon alpha-2a (PEG-IFN) and ribavirin (RBV) combination (IR group) treatment in the period from September 2nd, 2014 to February 1st, 2016 with patients previously untreated CHC enrolled to receive PEG-IFN, RBV, and sofosbuvir (SOF) combination (IRS group) in the period from August 2nd, 2015 to February 1st, 2016.

Treatment

Selected patients in IR group were assigned to receive 160 µgm of 20-kDa linear pegylated INF alpha-2a (Reiferon Retard®; Rhein-Minapharm Inc.) once a week for 48-weeks and ribavirin (Ribavirin®; Minapharm Inc.) 1000 mg/day for patients weighing< 75 kg and 1200 mg/day for patients weighing >75 kg. INF dose was reduced to 120 µgm/week if: ANC <750 /mm^3, PLT <50,000 /mm^3, Hg <8.5 g/dl. INF administration was temporarily suspended if ANC <500 /mm^3 and was permanently discontinued if ANC <350 /mm^3 or PLT <25,000 /mm^3. RBV dose was reduced to 600 mg/day if Hg <10 gm/dl.

Selected patients in IRS group were assigned to receive 400 mg of Sofosbuvir (Sovaldi®;Gilead Sciences, Inc.), 160 µgm of 20-kDa linear pegylated INF alpha-2a (Reiferon Retard®; Rhein-Minapharm Inc.) once a week for 12-weeks and ribavirin (Ribavirin®; Minapharm Inc.) 1000 mg/day for patients weighing <75 kg and 1200 mg/day for patients weighing >75 kg. INF dose was reduced to 120 µgm/week if: ANC <750 /mm^3, PLT <50,000 /mm^3, Hg <8.5 g/dl. INF administration was temporarily suspended if ANC <500 /mm^3 and was permanently discontinued if ANC <350 /mm^3 or PLT <25,000 /mm^3. RBV dose was reduced to 600 mg/day if Hg <10 gm/dl.

Monitoring

Patients were carefully monitored every week by physical examination with stress on treatment induced adverse effects together with laboratory parameters evaluations that included: complete blood picture (CBC),

aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, international normalized ratio (INR), serum creatinine, thyroid stimulating hormone (TSH) level, and alpha fetoprotein (AFP) level. Serum HCV-RNA levels were measured at 12th, 24th, 48th and 72nd weeks (IR group), or 4th, 8th, 12th and 24th weeks (IRS group) from starting treatment.

Virologic Assessment and Definition of Virologic Response

HCV-RNA was quantified by Amplicor Monitor Assay; Roch Molecular Systems. The specimen requirement for HCV-RNA by PCR is one EDTA Serum needs to be separated from cells within 6 hours of collection and refrigerated or frozen to avoid degradation of viral RNA. A DNA copy of viral RNA is synthesized by reverse transcription. This DNA molecule is amplified millions of times by PCR. The lower limit of detection for the assay was 0.6 KIU/ml.

For IR group the end of treatment response (ETR) as undetectable HCV-RNA at the end of the 48-week course of treatment; and sustained virological response (SVR) as undetectable HCV-RNA 24weeks after finishing treatment. For IRS group ETR defined as undetectable HCV-RNA at the end of the 12-week course of treatment; and SVR defined as undetectable HCV-RNA 12 weeks after finishing treatment. Patients had a detectable HCV RNA at any time after the ETR, had no viral load testing after the ETR and a detectable HCV-RNA on their last HCV viral load test while on treatment or died were considered non-responders and had to discontinue treatment according to hospital protocol. This was also done with patients who showed

Table 2. Clinical data of the studied patients

Parameter	IR Group			IRS GROUP			*P*-value	Sig.
	Mean ± SD	Range	CV%	Mean ± SD	Range	CV%		
Albumin (g/dl)	4.39 ± 0.44	3.10 –5.40	10.02	4.08 ± 0.40	3.30 –5.10	9.80	<0.001	Sig.
AST (IU/L)	66.07 ± 30.81	30 – 194	46.63	61.14 ± 35.10	12 –159	57.41	0.292	Ns.
ALT (IU/L)	67.39 ± 33.44	30 – 226	49.62	65.09 ± 55.24	13 – 323	84.87	0.723	Ns.
ALP (IU/L)	116.21 ± 43.84	44 – 243	37.72	110.84 ± 43.66	33 – 243	39.39	0.385	Ns.
AFP** (ng/ml)	4.70	0.20 – 120.50		5.10	0.5 – 35	197.34	0.057	Ns.
Total Bilirubin (mg/dl)	0.85 ± 0.35	0.38 – 3.00	41.18	0.82 ± 0.46	0.3 – 3.70	56.09	0.592	Ns.
Bilharzial Antibodies (+ve/-ve)*	22/75			25/80			0.850	Ns.
Scr (mg/dl)	0.76 ± 0.17	0.40 – 1.20	22.37	0.80 ± 0.193	0.54–1.70	24.1	0.095	Ns.
WBC (×1000/mm^3)	5.82 ± 1.72	2.70 – 10.40	29.55	5.99 ± 1.52	2.30–10.00	25.38	0.434	Ns.
Hb (g/dl)	13.89 ± 1.25	11.80 – 16.90	8.99	13.98 ± 1.71	11.30–16.90	12.23	0.698	Ns.
PLT (×1000/mm^3)	201.09 ± 704.49	80.00 – 450.00	350.34	182.33 ± 53.05	106.00 – 360.00	29.09	0.35	Ns.
TSH (mIU/L)	1.31 ± 1.05	0.20 – 4.56	80.15	1.54 ± 0.65	0.60 – 5.15	42.20	0.06	Sig.
Fasting Blood Glucose (mg/dl)	95.81 ± 31.11	60 –230	32.47	99.33 ± 27.59	64.00 – 225.00	27.78	0.394	Ns.
HbA1c, (%) if blood glucose > 26	6.8 ± 0.65 (n = 4)	6.10 –8.30	9.56	9.23 ± 2.13 (n = 21)	6.00 – 9.40	23.08	0.021	Sig.
Viral Load (KIU/ml)***	552.39 ± 757.44	0.10 – 4116.32	137.12	734.06 ± 173.10	1.46 – 14574.83	23.58	0.268	Ns.
METAVIR Fibrosis 0-2 / 3-4	70/27			46/59			<0.001	Sig.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; AFP: alpha fetoprotein; WBC: white blood cells; Hb: Hemoglobin; TSH: thyroid stimulating hormone; HbA1c; Glycated hemoglobin; SD: standard deviation; CV%: coefficient of variation. Positive reaction equal to or above 1/160. ** Results are reported as median. *** 1 KIU/ml = 900 copies/ml.*

reappearance of HCV-RNA while on treatment (breakthrough response). Relapse is defined as reappearance of HCV-RNA after finishing the course of treatment. Anti-viral efficacy was evaluated for all study patients using intention-to-treat analysis (ITT analysis).

Statistical Analysis

Results are presented as means ± standard deviations (SD) for continuous variables, median and range for non-normally distributed variables, and as frequencies and percentages for categorical data.

Analysis of normality was performed using the Kolmogorov-Smirnov test. Categorical data and proportions were analyzed using the $\chi 2$ test or the Fisher's exact test, as required. Student's t test was used to compare the means of the 2 groups with normal distributions, and the Mann-Whitney U test was used to compare variables with non-normal distributions.

All tests were 2-tailed. P-values <0.05 were considered statistically significant. Analysis was conducted using SPSS version 22.

RESULTS

A total of 202 adult Egyptian patients were selected from those patients who were enrolled for treatment of HCV at Ahmed Maher Teaching Hospital, divided into 2 groups; IR group composed of 97 patients enrolled to receive PEG-IFN and RBV combination, and IRS group composed of 105 patients enrolled to receive PEG-IFN, RBV, and Sofosbuvir combination.

Table 3. Treatment-related adverse events for each group

Treatment related AE, n (%)	IR Group n = 97	IRS Group n = 105	*P*-value	Sig.
General constitutional symptoms				
Fever	80 (82.47%)	69 (65.8%)	0.01	Sig.
Chills	23 (23.71%)	42 (40%)	0.016	Sig.
Fatigue	49 (50.52%)	87 (82.86 %)	<0.001	Sig.
Weight loss (>5% from baseline)	14 (14.43%)	16 (15.2%)	1.00	Ns.
Injection site reaction	26 (26.8%)	22 (20.9%)	0.408	Ns.
Gastrointestinal disorders				
Nausea	25 (25.77%)	20 (19.04%)	0.31	Ns.
Vomiting	13 (13.4%)	20 (19.04%)	0.342	Ns.
Abdominal Pain	16 (16.49%)	16 (15.2%)	0.849	Ns.
Anorexia	24 (24.74%)	30 (28.5%)	0.634	Ns.
Respiratory tract disorder				
Breathlessness	12 (12.37%)	14 (13.37%)	1.00	Ns.
Cough	13 (13.4%)	38 (36.2%)	<0.001	Sig.
Musculoskeletal disorders				
Arthralgia	10 (10.31%)	39 (37.1%)	0.0001	Sig.
Myalgia	24 (24.74%)	42 (40%)	0.0245	Sig.
Nervous system disorders				
Headache	54 (55.67%)	94 (89.52%)	0.0001	Sig.
Dizziness	14 (14.43%)	15 (14.23%)	1.00	Ns.
Psychological Disorders				
Nervousness & aggression	11 (11.34%)	26 (24.74%)	0.018	Sig.
Insomnia	29 (29.9%)	26(24.7%)	0.433	Ns.
Anxiety	10 (10.31%)	10 (<10%)	1.00	Ns.
Depression	22 (22.68%)	13 (12.3%)	0.0635	Ns.
Skin disorders				
Hair fall	29 (29.9%)	17 (16.2%)	0.0285	Sig.
Pruritus	17 (19.59%)	8 (<10%)	0.0526	Ns.

AE: Adverse events; Y: Years Old

Baseline Characteristics

The population in IR group studied comprised 79 (81.45%) males and 18 (18.55%) females; age ranged between 24 - 62 years with a mean age of 48.51 ± 8.01 years (Figure 1 shows the distribution of patients' age among different groups); also, weight ranged from 44 – 118 kg with a mean weight of 69.4 ± 12.23 kg. The population in IRs group studied comprised 62 (59.04%) males and 43 (40.95%) females; age ranged between 35-62 years with a mean age of 49 ± 7.26 years (Figure 1 shows the distribution of patients' age among different groups); also, weight ranged from 40-100 kg with a mean weight of 73.97 ± 11.39 kg. Table 1 summarizes the baseline demographic and table 2 summarizes the clinical data for the studied population of both groups.

Adverse Events (AEs)

In IR group all patients had at least one AE during treatment. Most treatment-related AEs were considered mild or moderate in severity and were consistent with flu-like symptoms such as fever, headache, and fatigue. All AEs reported are summarized in (Table 3). In IRS group patients suffer from same symptoms as in IR group but headache and fatigue more predominant in IRS group as summarized in (Table 3).

Table 4. Treatment related laboratory abnormalities

	Nadir, mean ± SD			Change from baseline, mean ± SD			Sig.
Laboratory test	IR group	IRS group	p-value	IR group	IRS group	*P*-value	
ANC (cells/mm^3)	1686.32 ± 571.56	1900.08 ± 888.95	0.042	-1433.35 ± 841.66	-3180.28 ± 1668.38	0.985	Ns.
Hb (g/dl)	9.84 ± 1.13	9.75 ± 0.95	0.572	-4.21±1.55	-3.45 ± 1.91	<0.001	Sig.
PLT (×1000/mm^3)	125.70 ± 41.67	117.22± 37.86	0.131	-71.686± 57.56	-69.44 ± 54.82	0.776	Ns.

*ANC: Absolute Neutrophilic Count; Hb: Hemoglobin; PLT: Platelets; TSH: Thyroid Stimulating Hormone. * Results are reported as zenith.*

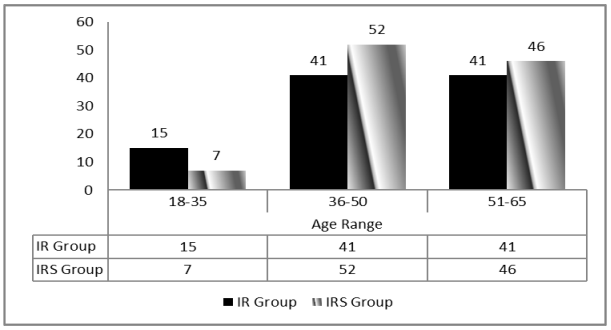
Table 5. Adverse events leading to dose reduction or interruption

	IR group			IRS group			*P*-value	Sig.
Adverse Event	Frequency, n (%)	Management	SVR rate, n (%)	Frequency, n (%)	Management	SVR rate, n (%)		
Anemia	59 (60.82)	47 RBV dose reduction	30 (63.83)	20 (19.05)	20 RBV dose reduction	14 (70)	0.839	Ns.
		12 RBV & IFN dose reduction	7 (58.33)					
Neutro-penia	4 (4.12)	1 Treatment Discontinuation	1 (100)	1	1 Treatment Discontinuation	1 (100)	1.00	Ns.
		1 Suspended IFN	0 (0)					
		2 IFN dose reduction	2 (100)					
Thrombo-cytopenia	1 (1.03)	IFN dose reduction	1 (100)	0			1.00	Ns.
Fundal Hemorrhage	1 (1.03)	Treatment discontinuation	0 (0)	0			1.00	Ns.
Death	1 (1.03)	N/A	0 (0)	0				

SVR: Sustained Virological Response; IFN: Interferon; RBV: Ribavirin; N/A: Not Applicable.

Clinical Laboratory Evaluation

In IR group most changes in laboratory values were classified by WHO criteria.[26] Table 4 summarizes laboratory abnormalities encountered during treatment. Grade 3 (500 to <750/mm^3) and grade 4 (<500/mm^3) neutropenia occurred in 3 (3.1%) and 2 (2.1%) patients, respectively. One of the patients with grade 4 neutropenia discontinued treatment at week 32 (ANC 345/mm3) but achieved an SVR, and the other had improved counts when re-tested and was managed with suspending PEGIFN alpha-2a doses for 2 weeks. Grade 2 thrombocytopenia (PLT 50,000 – 75,000/mm^3) occurred in 10 patients (10.3%), and only one patient (1.03%) had grade 3 (49,000/mm^3) that was managed by PEG IFN alpha-2a dose reduction. The magnitude of reductions in hemoglobin (Hb) concentration from baseline was similar in all age groups. At nadir, the mean change from baseline was - 4.21 ± 1.55 g/dl. Anemia was managed through dose reduction of RBV in 47 (48.45%) patients and 12 patients (12.37%) required both PEGIFN alpha-2a and RBV dose reduction.



	18-35	36-50	51-65
IR Group	15	41	41
IRS Group	7	52	46

Figure 1. Distribution of patients' age among different groups

In IRS group, at nadir, the mean change from baseline of Hb is -3.45 ± 1.91 g/dl. Anemia was managed through dose reduction of RBV in 20 (19.05%) patients and one patient (0.95%) requires PEGIFN alpha-2a reduction. (Table 5) summarize Adverse events leading to dose reduction or interruption in both groups.

Virological Response

In IR group Twenty-two (22.68%) patients were non-responders, whereas 75 (77.32%) patients attained early virological response (EVR) of whom 62 (63.92%) had ETR and 13 (13.4%) had a breakthrough response. Of the 62 patients with ETR, 11 (11.34%) had a relapse while 51 (52.58%) patients achieved SVR.

In IRS group six (5.72%) patients were non-responders, where as 99 (94.28%) patients attained ETR of whom 29 (27.62%) had a relapse while 70 (66.67%) patients achieved SVR; Figure 2 summarizes patient response according to treatment.

Factors associated with SVR were assessed using variables in Table 1. Significant factors in IR group included: age, baseline viral load, baseline METAVIR fibrosis score, AST, ALT, ALP, AFP, TSH and WBC.

In IRS group: age, baseline viral load, baseline METAVIR fibrosis score, AST, ALT, Serum creatinine, Hemoglobin. Table 6 summarizes factors affecting response in each group.

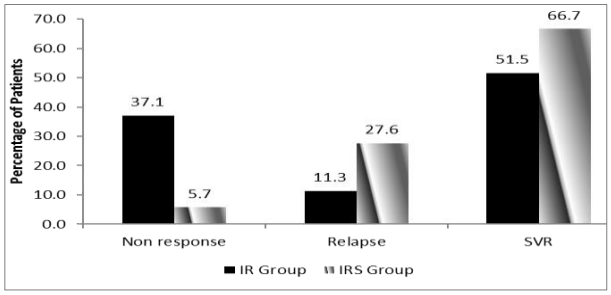


Figure 2. Patients response according to treatment

DISCUSSION

Here, we present a "real-world data" cohort of patients who were treated for chronic HCV4 infection with 12 weeks treatment of SOF/IFN/RBV (IRS group) compared to cohort of patients treated with old standard IFN/RBV (IR group) for 48 weeks. There are a few head to head comparisons such our study in literature. Real-world data about the safety and efficacy of SOF/IFN/RBV combination in HCV genotype 4 are limited. In the registration trial *(NEUTRINO trial)* by[25]. Only 28 treatment-naïve patients with HCV genotype 4 infections were enrolled. The SVR frequency among this subgroup was 96.4% which is obviously greater than our reported frequency of 66.67%, also our study largely differs from result of *Wehmeyer et al*[27], which report that patients receiving SOF/IFN/RBV achieve 100% SVR which reflects that data obtained from clinical trials are not always reproducible in real clinical settings. Most important explanation of difference in result between our study (IRS group) and studies of both *Lawitz et al* and *Wehmeyer et al* that we study on large number of patient (N=105), on other hand they study on 28, 24 respectively. The IR group analysis revealed that SVR 52.58% so treatment of patients with old standard IFN/RBV treatment at increased risk for a virological failure than IRS group, one of important factor that may significantly affect response of IFN/RBV in IR group is adherence because of longer duration (48 weeks) of therapy. It is also found that the SVR rate decreases significantly with increasing age and Metavir fibrosis score in both groups. This indicates that higher SVR rates are expected in younger adults with low Metavir fibrosis score (0-2) than older patients with more advanced fibrosis and starting therapy for aged patient with advanced fibrosis may not be preferred to decrease costs and unnecessary drug exposure and adverse effects. Several studies reported

Table 6. Factors affecting response in each group

Factor		Viral Response		*P*-value	*Sig*	Viral Response		*P*-value	Sig
		SVR	Non-SVR			SVR	Non-SVR		
Age	18-35	14	2	0.003*	Sig.	2	0	0.015*	Sig.
	36-50	23	20			37	20		
	51-65	14	24			31	15		
Sex	Male	43	36	0.444	Ns.	42	20	0.779	Ns.
	Female	8	10			28	15		
Baseline Viral Load*** (KIU/ml)	Very low**	10	2	0.002*	Sig.	2	3	0.009*	Sig.
	Low**	17	6			23	4		
	Moderate**	20	26			33	20		
	High**	4	12			12	10		
METAVIR fibrosis	0-2	28	42	0.018*	Sig.	37	10	0.023*	Sig.
	3-4	9	18			33	25		
Albumin (gm/dl)		4.41 ± 0.46	4.39 ± 0.42	0.823	Ns.	4.09 ± 0.39	4.05 ± 0.43	0.381	Ns.
AST (IU/L)		55.53 ± 20.32	69.174 ± 37.16	0.03*	Sig.	55.41 ± 32.78	76.4 ± 39.64	0.009*	Sig.
ALT (IU/L)		60.21 ± 17.59	75.35 ± 43.80	0.033*	Sig.	57.28 ± 41.94	98.48 ± 67.44	0.002*	Sig.
ALP (IU/L)		105.65 ± 36.42	127.91 ± 48.57	0.012*	Sig.	114.57 ± 41.48	103.40 ± 47.47	0.218	Ns.
Total bilirubin**** (mg/dl)		0.84 ± 0.27	0.85 ± 0.43	0.878	Ns.	0.79 ± 0.42	0.86 ± 0.54	0.487	Ns.
Serum creatinine**** (mg/dl)		0.75 ± 0.18	0.76 ± 0.16	0.716	Ns.	0.84 ± 0.84	0.73 ±0.13	0.003*	Sig.
TSH**** (mIU/L)		1.44 ± 1.13	1.08 ± 0.78	0.067	Ns.	1.98 ± 1.26	2.04 ± 1.13	0.837	Ns.
WBC (/mm^3)		5440.78 ± 1556.41	6228.70 ± 1810.17	0.023*	Sig.	5988.50 ± 1492.49	6000.63 ± 1598.44	0.964	Ns.
Hemoglobin (gm/dl)		13.91 ± 1.41	13.88 ± 1.05	0.889	Ns.	14.25 ± 1.66	13.44± 1.69	0.022*	Sig.
Platelets (/mm^3)		210149.02 ± 80281.83	191043.48 ± 56838.94	0.184	Ns.	180385.7 ± 6018.36	186200 ± 65491.27	0.893	Ns.
AFP*** (ng/ml)		4.0	6.40	0.001*	Sig.	6.076	6.4	0.482	Ns.

*SVR: sustained virological response; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; TSH: thyroid stimulating hormone; WBC: white blood cells; AFP: alpha feto protein. * Statistically significant difference between SVR and non-SVR groups. ** Very low < 10 KIU/ml, low < 100 KIU/ml, moderate < 1000 KIU/ml, high > 1000 KIU/ml. *** Results are reported as median and Mann-Whitney U test was used to detect significance. **** Effect may be unclear because all patients had a normal baseline values.*

that SVR rate varies significantly by sex.[28-32] However, the effect of sex was non-significant in our study. An interesting finding in IR group study is that patients received lower doses of RBV or RBV/IFN due to AEs had an unexpected significantly higher SVR rate than those who received full doses. This finding may be due to higher plasma RBV level in some patients that led to more AEs necessitating dose reduction. But in IRS group patients who required RBV and RBV/IFN dose reduction due to AEs had a non-significant SVR rate than those than those who received full dose of RBV and IFN because of shorter duration of therapy in IRS group than IR group.

The safety and tolerability issues reported in IR study is different from that reported by *Esmat et al*.[33] We report a 60.82% frequency of anemia (Hb <10 gm/dl), 4.12% for neutropenia (ANC <750 /mm^3), one case of IFN dose reduction due to thrombocytopenia, one case of death, and 2 cases of treatment discontinuation due to AEs. On the other hand, *Esmat et al*. reported a 6% frequency of anemia, 9% for neutropenia, and no dose reduction or treatment discontinuation due to AEs although the studied sample is of similar size (n = 100).

Also it found that safety results of SOF/IFN/RBV are significantly more tolerable than 48 weeks of IFN/RBV. The frequency of severe anemia, thrombocytopenia and leucopenia, as well as the need for ribavirin dose adjustment was more common during 48 weeks of IFN/RBV compared to the shorter12-week SOF/IFN/RBV treatment regimen, which indicates the impact of the reduced time-span of PEG-IFN toxicity in SOF-based triple therapy.

CONCLUSION

This new combination containing Sofosbuvir more effective and tolerable than old standard therapy, but still ineffective enough so that more researches and treatment combination needed to combat hepatitis C epidemic in Egypt. The response to Sofosbuvir, PEGINF alpha-2a and RBV combination in CHC Egyptian patients varies depending factors including: age, baseline fibrosis stage, ALT, AST, Scr, and Hb. Knowledge of these factors is important for individualized patient treatment decisions and to determine patients' priority treatment in case of scarce financial resources allocation.

Conflict of Interest: The authors declare that they don't have any conflict of interest

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