Efficacy and Safety of Peg-Interferon/Sofosbuvir/Ribavirin VS Sofosbuvir/Simeprevir in Egyptian chronic hepatitis C patients

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Background and study aim: Recently, multiple regimens of different direct-acting antiviral agents (DAAs) have been emerged. We aimed to assess the efficacy, safety and improvement of liver profile for patients treated with regimens of direct acting-antivirals in Egypt.

Patients and Methods: A retrospective observational study was conducted at Suez governorate, including a simple random sample of 76 patients treated with directly-acting antiviral therapy and came to our center to enroll our follow up program after antiviral therapy from November 2015 to May 2016. Sustained viral response (SVR) was established at week 12 after end of treatment.

Results: A total of 76 chronic hepatitis C patients initiated treatment with DAAs. Forty patients (52.6%) were treated with triple therapy and thirty-six patients (47.3%) with dual therapy. All patients were treated for 12 weeks. According to Intention to treat analysis, 35 of 40 patients (87%) who treated with triple therapy achieved SVR while 32 of 36 patients (88.9%) treated with dual therapy achieved SVR. However, the difference between responders after both regimens wasn't statistically significant (p= 1). In the group treated with triple therapy, significantly more patients had anemia, leukopenia and thrombocytopenia with no serious side effects leading to discontinuation of therapy.

Conclusion: Both regimens had similar efficacy, but the dual therapy was more tolerated with less side effect profile.

INTRODUCTION

Hepatitis C virus (HCV) is a worldwide problem. Globally, it was estimated that in 2005, more than 185 million people had hepatitis C virus (HCV) antibodies (prevalence of 2.8 percent) **[1]**. The condition has been worsened in Egypt as it has the highest HCV prevalence in the world **[2]**. In 2008, an Egyptian Demographic Health Survey (EDHS) determined a prevalence of 14.7% for sampled population 11125 had positive antibodies to HCV, however only 9.8% were found to have HCV RNA **[3]**. Recently, Egyptian Health issues Survey (EHIS) in 2015 estimated a prevalence of 10% for sampled population 26172 had positive antibodies to HCV, however only 7% were found to have HCV RNA **[4]**. HCV also represents an economic burden in Egypt which will continue over the next decade **[5]**.

As far as 2011, the combination of pegylated interferon and ribavirin for 48 weeks was the effective treatment for chronic hepatitis C, but several HCV direct-acting antiviral agents (DAAs) have been approved in 2014 for HCV infection so many DAA agents have been licensed as the standard treatment now **[6]**.

We aimed to assess the efficacy, safety and improvement of liver profile for patients treated with Peg- triple therapy (Peg-Interferon/Sofosbuvir/Ribavirin) VS dual therapy (Sofosbuvir/Simeprevir) regimens. These regimens represented the first early experience of Egyptian chronic hepatitis C patients with DAAs.

PATIENTS AND METHODS

Study design:
A retrospective observational study was conducted in Communicable Diseases Research and training Center (affiliated with Suez Canal University hospitals) at Suez governorate from November 2015 to May 2016.

Population and sample:
Target population:
Chronic hepatitis C patients treated with Sofosbuvir-based regimens included dual therapy, Simeprevir & Sofosbuvir and triple therapy, Pegylated interferon, Sofosbuvir and Ribavirin in Egypt.

Study sample:
A simple random sample of 76 patients was selected from total 559 patients treated with directly-acting antiviral therapy and came to our center to enroll our follow up program after antiviral therapy.

Criteria of selection:
All patients enrolled in this study were previously diagnosed as chronic hepatitis C patients aged 18-70 years and had Fib 4 more than 2.5.All patients which had decompensated liver diseases, hepatocellular carcinoma, extra-hepatic malignancy and uncontrolled diabetes mellitus (HbA1c >8%) were excluded. All these criteria were according to the protocol provided by national committee for control of viral hepatitis in Egypt (NCCVH) in May 2015.

Assessment
HCV RNA was assessed at all patients 12 weeks and 24 weeks after therapy completion using Cobas AmpliPrep/Cobas TaqMan HCV Test, Version 2.0, Real-Time PCR assay, Roche Molecular Systems, with a Low detection limit of 15 IU/mL and a linear amplification range of HCV RNA from approximately 15 to 10 000 000 IU/ mL. CAP/CTM HCV v2.0 assays.

Ethics
The study was approved by the Ethics Committee of Suez Canal University Faculty of Medicine. Written, informed consent was obtained from each patient included in this study.

Statistical analysis
Statistical analyses were performed using the statistical software package SPSS for Windows, version 19 (SPSS, IBM Inc., NC, USA). Baseline demographic and clinical characteristics were analyzed descriptively for all patients. Categorical variables were expressed as frequency and percentage while the continuous variables were expressed as mean and standard deviation. We used the Mann–Whitney *U*-test, the Fisher's exact test and student's t test where appropriate. Differences were considered statistically significant when $P<0.05$. Statistical analysis will be performed using SPSS version 19 (SPSS, IBM Inc., NC, USA).

RESULTS

Treatment response, predicators and side effect profile
Baseline characteristics between patients treated with both regimens who achieved SVR and non-responders were described and there were no significant differences between them. (Table 1,2)

According to Intention to treat analysis, 35 of 40 patients (87%) who treated with triple therapy (Peg-IFN/SOF/RBV) achieved SVR. While 32 of 36 patients (88.9%) treated with dual therapy (SIM/SOF) achieved SVR. However, the difference between responders after both regimens wasn't statistically significant (p= 1) (Table 3).

Multivariate logistic regression analysis was done in patients treated with triple therapy (Peg-IFN/SOF/RBV) and dual therapy (SIM/SOF); with the failure of response was dependent variable. In patients treated with triple therapy, male gender, patients with previous interferon therapy and viral load >600 000 IU were 1.1, 7.2 and 5.2 times less likely to respond, respectively. Moreover, in patients treated with dual therapy, males, patients with previous interferon therapy and viral load > 600 000 IU were 1.2, 2.2 and 1.8 times less likely to respond, respectively (Table 4). However, the model was statistically insignificant for both groups (P = 0.056 and P = 0.872, respectively).

In the group treated with triple therapy, significantly more patients had anemia, leukopenia and thrombocytopenia with no serious side effects leading to discontinuation of therapy (Table 5).

Follow up laboratory assessment during and 12 weeks after therapy
In patients treated with triple therapy (Peg-INF/ SOF/RBV), ALT levels improved significantly until week 12 post-treatment (89.05 ± 41.87 IU/ ml at baseline vs. 46.15 ± 39.91 IU/ml at week 12 post-treatment; P<0.05). Moreover, AST levels also improved significantly at the same time point (93.05 ± 32.83 IU/ ml at baseline vs. 50.87

± 41.11 IU/ml at week 12 post-treatment; P = 0.106). However, the levels of Hemoglobin steeping decreased significantly after therapy (13.59 ± 1.51 g/L at baseline vs. 11.62 ± 1.51 g/L at week 12 post-treatment; P<0.05). Moreover, the levels of platelet count significantly decreased as follow: (151.35 ± 32.46 × 10^3/mm^3 at baseline vs. 125.5 ± 37.85 × 10^3/mm^3 at week 12 post-treatment; P < 0.05). Also, WBCs count as follows: (6.12 ± 1.75 /mm^3 at baseline vs. 4.77 ± 1.87 /mm^3 at week 12 post-treatment; P<0.05). (Figure 1 & 2).

In patients treated with dual therapy (SIM/SOF), ALT levels normalized during and after therapy (67.78 ± 35.14 IU/ ml at baseline vs. 21.94 ± 10.71 IU/ml at week 12 post-treatment; P < 0.05). Also, AST levels normalized as follow: (71.5 ± 35.57 IU/ ml at baseline vs. 25.58 ± 8.72 IU/ml at week 12 post-treatment; P<0.05). Moreover, the Platelet count improved significantly during therapy until week 12 post-treatment (108.47 ± 38.56 × 10^3/mm^3 at baseline vs. 120.64 ± 45.14 × 10^3/mm^3 at week 12 post-treatment; P<0.05). However, the hemoglobin levels decreased significantly after therapy as follow: (13.58 ± 1.27 g/L at baseline vs. 12.68 ± 1.78 g/L at week 12 post-treatment; P<0.05) (Figure 3 & 4).

Table (1): Sustained virological response (SVR12) and predicators of response in patients treated with triple therapy (Peg-INF/SOF/RBV).

Parameter	SVR n= 35 (87.5%)	Non-SVR n= 5 (12.5%)	P value
Age (years) (mean ± SD)	56.86±6.35	53.2±4.82	.103
Sex [male : female]	19:16	3:2	1
Body mass index (Kg/m^2) (mean ± SD)	30.63±4.75	30.2±2.49	.751
Smokers (%)	2 (5.7)	1 (20)	.338
Diabetes mellitus (%)	12 (34.3)	1 (20)	1
Previous treatment failure (%)	4 (11.4)	1 (20)	.507
Current type of Interferon (INF) INF alpha-2a (%) INF alpha-2b (%)	 16 (45.7) 19 (54.3)	 3 (60) 2 (40)	.654
Hemoglobin (g/dl) (mean ± SD)	13.63±1.5	13.28±1.43	.605
White blood cell count (/mm^3) (mean ± SD)	5.98±1.77	7.08±1.27	.157
Platelets(X 10^3/mm^3) (mean ± SD)	153.4±31.69	137±37.98	.228
ALT (IU/ml) (mean ± SD)	91.57±42.07	71.4±40.34	.298
AST (IU/ml) (mean ± SD)	96.31±32.74	70.2±25.52	.113
Bilirubin (mg/dl) (mean ± SD)	0.93±0.28	0.79±0.41	.449
Albumin (g/dl) (mean ± SD)	4.02±0.34	3.84±0.22	.244
INR	1.15±0.17	1.17±0.05	.498
AFP (ng/ml) (mean ± SD)	10.29±6.86	14.54±11.82	.498
Fib 4 score	3.89±1.03	3.53±0.85	.498
Splenomegaly (%)	14 (40)	2 (40)	1

(SVR) sustained virological response, (ALT) alanine aminotransferase (AST) aspartate aminotransferase, (INR) international normalized ratio, (AFP) alpha-fetoprotein, (HCV) hepatitis C virus, (SD) standard deviation

Table (2) : Sustained virological response (SVR12) and predicators of response in patients treated with dual therapy (SIM/SOF)

Parameter	SVR n= 32 (88.9%)	Non-SVR n= 4 (11.1 %)	P value
Age (years) (mean ± SD)	57.78±7.45	58.5±3	1
Sex [male : female]	21:11	3:1	1
Body mass index (Kg/m^2) (mean ± SD)	30.33±5.18	27.25±2.75	.208
Smokers (%)	5 (15.6)	1 (25)	.535
Diabetes mellitus (%)	12 (37.5)	0	.278
Previous treatment failure (%)	4 (12.5)	0	1
Hemoglobin (g/dl) (mean ± SD)	13.58±1.35	13.55±0.59	.610
White blood cell count ($/mm^3$) (mean ± SD)	4.66±1.47	4.65±1.93	1
Platelets(X $10^3/mm^3$) (mean ± SD)	108±39.66	107.25±33.12	.942
ALT (IU/ml) (mean ± SD)	64.31±31.29	95.5±55.99	.248
AST (IU/ml) (mean ± SD)	66.37±27.2	112.5±67.79	.19
Bilirubin (mg/dl) (mean ± SD)	0.95±0.42	1.45±1.07	.366
Albumin (g/dl) (mean ± SD)	3.77±0.58	3.52±0.46	.393
INR	1.24±0.18	1.29±0.11	.315
AFP (ng/ml) (mean ± SD)	10.42±6.07	19.17±12.79	.173
Fib 4 score	5.2±3.09	6.54±2.76	.340
Splenomegaly (%)	25 (78.1)	1 (25)	.057

(SVR) sustained virological response, (ALT) alanine aminotransferase, (AST) aspartate aminotransferase, (INR) international normalized ratio, (AFP) alpha-fetoprotein, (HCV) hepatitis C virus, (SD) standard deviation

Table (3): Sustained virological response in all patients according to received regimens of antiviral therapy

Type of Regimen	SVR 12 (%)		P value
	SVR	Non-SVR	
Peg-INF/SOF/RBV	35 (87)	5 (12)	1
SIM/SOF	32 (88.9)	4 (11.1)	

(SVR) sustained virological response, (SOF) Sofosbuvir, (INF) Interferon, (RBV) Ribavirin, (SIM) Simeprevir

Table (4): In multivariate logistic regression, in which dependent variable is the treatment failure in patients treated with both regimens

Baseline Characteristics	Triple therapy		Dual therapy	
	OR (CI 95 %)	P value	OR (CI 95 %)	P value
Male gender	1.1 (.07- 16.9)	0.93	1.2 (.09 – 15.4)	0.87
Previous treatment failure	7.2 (.8 – 64.3)	0.07	2.2 (.16 – 32.1)	0.55
Viraemia > 600 000 IU	5.2 (.4 – 64.7)	0.2	1.8 (.17 – 20.2)	0.62

Table (5) : Side effect profile in all patients according to received regimens of antiviral therapy

Side effect	Overall (%)	Peg-INF/SOF/RBV (%)	SIM/SOF (%)	P value
Pseudo-flu syndrome	3 (3.9)	3 (7.5)	0	.242
Respiratory disorders	6 (7.9)	6 (15)	0	.026
Headache	2 (2.6)	2 (5)	0	.495
Skin rash	1 (1.3)	1 (2.5)	0	1
GI Symptoms	4 (5.3)	4 (10)	0	.117
Anemia	30 (39.5)	24 (60)	6 (16.7)	.000
leukopenia	26 (34.2)	22 (55)	3 (8.3)	.000
Thrombocytopenia	22 (28.9)	19 (47.5)	4 (11.1)	.000
Elevated bilirubin	13 (17.1)	7 (17.5)	6 (16.7)	1
Elevated ALT	6 (7.9)	5 (12.5)	1 (2.8)	.204
Elevated AST	1 (1.3)	1 (2.5)	0	1

(SOF) Sofosbuvir, (Peg-INF) Pegylated Interferon (RBV) Ribavirin, (SIM) Simeprevir, (ALT) alanine aminotransferase, (AST) aspartate aminotransferase

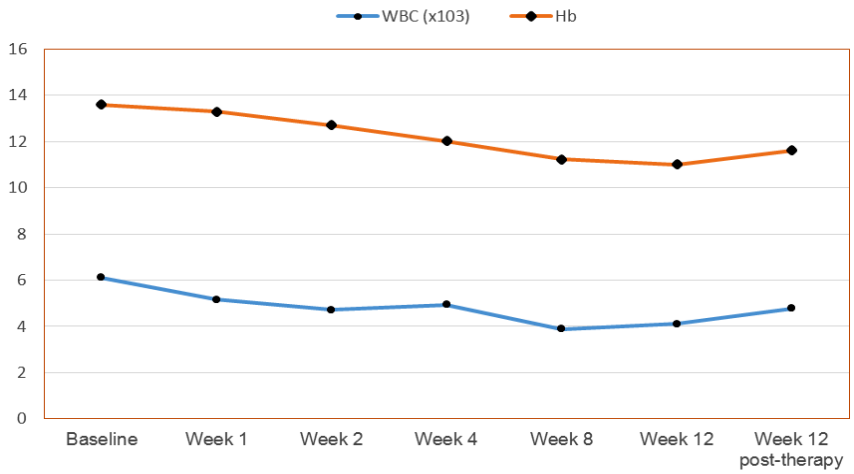

Figure 1. Hematological changes regarding WBC (x103) & Hemoglobin levels (gm/dl) at baseline and follow-up assessments during and 12 weeks post-end of Peg-INF/RIB/ SOF therapy (N=40)

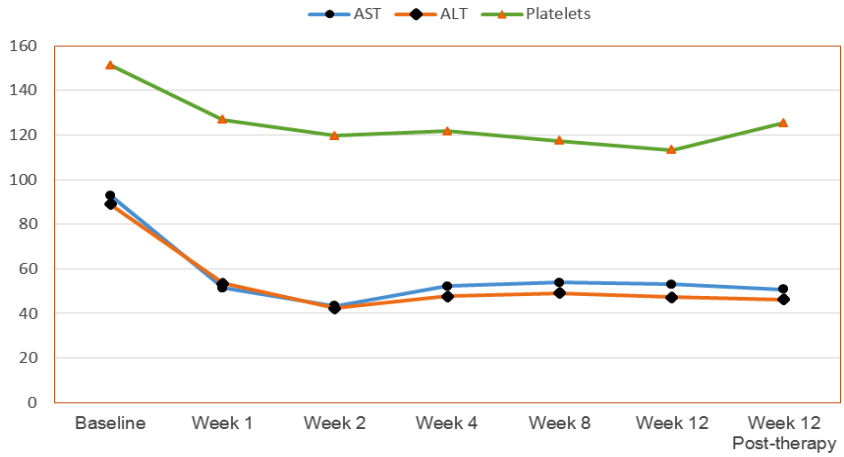

Figure 2. Changes in AST, ALT & Platelets (x103) at baseline and follow-up assessments during and 12 weeks post-end of Peg-INF/RIB/ SOF therapy (N=40)

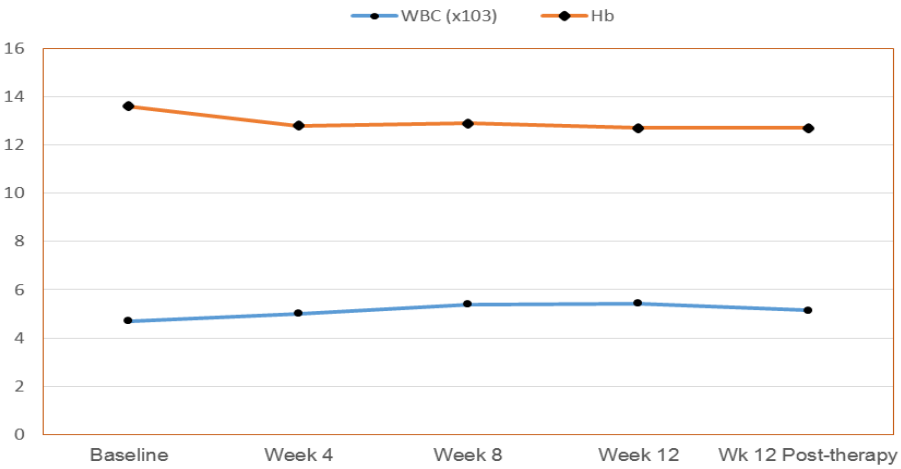

Figure 3. Hematological Changes regarding WBC (x103) & Hemoglobin level (gm/dl) at baseline and follow-up assessments during and 12 weeks post-end of SIM/SOF therapy (N=36)

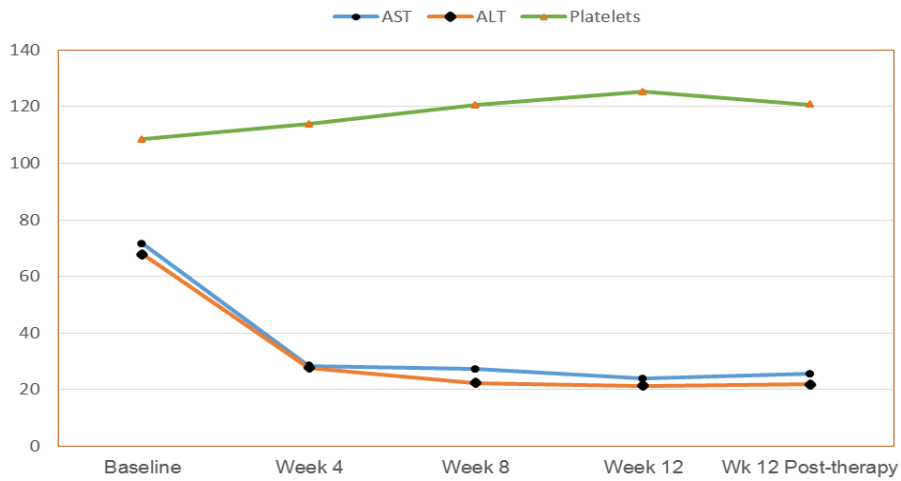

Figure 4. Changes in AST, ALT & Platelets (x103) at baseline and follow-up assessments during and 12 weeks post- end of SIM/SOF therapy (N=36)

DISCUSSION

In this study 76 patients with proven chronic hepatitis C which were treated for 12 weeks by DAAs. Forty patients (52.6%) were treated with triple therapy (Peg-INF/SOF/RBV) and SVR12 rate was 87% while thirty-six patients (47.3%) were treated with dual therapy (SIM/SOF) and SVR12 rate was 88.9%.

A retrospective multicentric study conducted in Egypt on 8742 chronic hepatitis C patients with compensated cirrhosis treated with triple therapy (Peg-INF/SOF/RBV) for 12 weeks and the SVR12 rate was 94%. The SVR12 in this cohort is slightly higher than my study as all 76 patients included in my study have high FIB4 (3.85 ± 1) in comparison to this cohort (3.08 ± 7.6) **[7]**.

A single centered, nonrandomized, uncontrolled phase 2 study conducted at Texas on 47 treatment-experienced patients with HCV genotypes 2 and 3. All these patients treated for 12 weeks with triple therapy (Peg-INF/SOF/RBV) and the overall SVR12 rate was 89%, but for genotype 3, the SVR 12 was 83% **[8]**.

In the phase 2 trial (LONESTAR-2 trial) using a 12 week regimen of triple therapy (Peg-INF/SOF/RBV), SVR12 rate was 89% among 47 treatment-experienced patients with chronic HCV genotype 2and 3 infection, so that the EASL guidelines 2015 recommended this combination of as a first option in patients with genotype 3 **[9]**.

A randomized multicenter phase 2 trial (ATOMIC) reported that 82% of patients with genotype 4 who treated with triple therapy achieved SVR12 **[10]**. Moreover, a randomized, double-blind trial (phase 2) in USA stated that SVR12 rate among 47 patients with genotypes 1, 2 and 3 was 91% **[11]**. It is notable that our study had SVR12 close to SVR12 rate of these phase 2 clinical trials. However, the NEUTRINO study (phase 3) reported higher SVR12 than our study which was 96% among patients with genotype 4 **[12]**.

A multicenter cohort study in Egypt stated that the overall SVR12 rate was 95% in 583 chronic hepatitis patients treated with 12 week regimen of dual therapy (SIM/ SOF). Moreover, The SVR12 rates in both naïve patients and those with previous interferon treatment were 94% to 99% for mild to moderate fibrosis (F1-F3) and 80% to 90% for advanced fibrosis (F4), respectively **[13]**.

Another Egyptian cohort study conducted on 6211 chronic HCV genotype 4 patients found the SVR 12 rate was 97% after 12 week regimen of dual therapy (SIM/SOF). Moreover, SVR 12 rates in easy and difficult to treat (patients with Fib 4 index >3.25 and METAVIR score F3- F4) groups were 96% and 93% respectively **[14]**. In our study had close SVR 12 rate to the patients with advanced fibrosis in the previous two Egyptian studies **[13,14]**.

A retrospective study from Netherlands assessed the SVR 12 for 53 patients with genotype 4 HCV infection treated with dual therapy (SIM/SOF) with or without ribavirin which was 92% **[15]**. This SVR12 was slightly higher than our result which might be explained by addition of ribavirin in the Dutch study as they reported that all relapsed patients didn't receive ribavirin **[15]**.

The OSIRIS trial studied effectiveness of simeprevir plus sofosbuvir for eight or 12 weeks in 63 chronic hepatitis C virus (HCV) genotype 4 patients with METAVIR F0-F4 fibrosis. Accordingly, the overall SVR was 92% while the SVR in 23 patients with compensated cirrhosis (METAVIR F4) received 12 weeks of treatment was 100% which higher than my study **[16]**.

The OPTIMIST-1 reported efficacy of dual therapy (SIM/SOF) for 12 weeks in 133 chronic hepatitis C virus (HCV) genotype 1 patients without cirrhosis (METAVIR F0-F3). Hence, the SVR12 was 97% which higher than our study due to lower fibrosis stage in patients included in the OPTIMIST-1 **[17]**.

However, the efficacy of Simeprevir 150 mg and Sofosbuvir 400 mg once daily for 12 weeks in 103 chronic hepatitis C virus (HCV) genotype 1 patients with cirrhosis was accessed in the OPTIMIST-2 study **[18]**. Accordingly, the SVR12 was 83% in the OPTIMIST-2, which close to my study.

A single center study conducted at Miami, US reported the SVR12 for 86 chronic hepatitis C virus (HCV) genotype 1 patients with confirmed cirrhosis (About 60% of them was cirrhotic and METAVIR score was F4) treated with dual therapy (SIM/SOF) and 12 other patients treated with triple therapy (Peg-INF/SOF/RBV). Accordingly, the SVR12 for dual therapy was 88%, which agree with our results. However, the SVR12 for triple therapy was 50% which was much lower than our results **[19]**.

Also, a single center study at Atlanta, US found that chronic hepatitis C virus (HCV) genotype 1 patients treated with dual therapy (SIM/SOF) for 12 weeks had a significantly higher rate of SVR12 than those treated with triple therapy (Peg-INF/SOF/RBV) **[20]**. In this study, a 12 week regimen of dual therapy also had a higher rate of SVR12 than a 12 week regimen of triple therapy, but unfortunately not significant.

In our current study, males, patients with previous Interferon therapy and high viral load less likely to achieve SVR12, but all of these baseline characteristics were statistically insignificant as predicators for treatment failure in both univariate and multivariate analysis. Similar results were reported by Christina et al, who reported baseline characteristics included age, BMI, high viral load, cirrhosis, prior treatment and ethnicity were no longer predicative factors for treatment failure except male gender in directly acting antiviral therapy **[21]**.

In contrast, female gender, higher baseline platelets and grades of fibrosis were predicators for SVR12 in 583 chronic hepatitis C genotype 4 patients treated with dual therapy (SIM/SOF) **[13]**. Also, a large cohort observational study in Egypt reported that male gender, higher baseline viraemia and previous treatment failure were predicative factors for treatment failure in 14, 409 chronic hepatitis C genotype 4 patients

treated with triple therapy (Peg-INF/SOF/RBV) **[7]**.

In this study, liver enzymes improved significantly in patients treated with both regimens while the platelet count improved only in patients treated with dual therapy (SIM/SOF). This agreed with German study which reported improvement of liver function during directly acting antiviral therapy regardless of HCV genotype **[22]**. Moreover, Dutch study stated that platelet count improved in decompensated hepatic fibrosis patients following SVR after interferon-based therapy which correlated with decreased spleen size as portal pressure might be improved by HCV eradication **[23]**.

In our study, Dual therapy (SIM/SOF) and triple therapy (Peg-INF/SOF/RBV) were well tolerated in patients evaluated. Notable side effects in patients treated with triple therapy included pseudo-flu syndrome in 7.5%, respiratory disorders in 15%, headache in 5%, skin rash in 2.5%, GI symptoms in 10%, anemia in 60%, thrombocytopenia in 47.5%, and hyper-bilirubinemia in 17.5%. Furthermore, mild side effects also noted in patients treated with dual therapy included anemia in 16.7%, thrombo-cytopenia in 11.1%, and hyperbilirubinemia in 16.7%.

Similar side effect profile reported in other studies which evaluated the patients treated with triple therapy also included pseudo-flu syndrome, headache, skin rash, GI symptoms, anemia, thrombocytopenia, and hyperbilirubinemia (Lawitz et al., 2013a; Lawitz et al., 2015a; Wu et al., 2015). Moreover, the most reported adverse events in patients treated with dual therapy included anemia, thrombocytopenia and hyper-bilirubinemia with no serious adverse effects leading to discontinuation of treatment **[13,17]**.

In conclusion, both regimens had similar efficacy, but the dual therapy was more tolerated with less side effect profile.

Ethical consideration

This research was approved by the Ethics committee at Faculty of Medicine, Suez canal university in February 2016

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