Addition of Sofosbuvir to the Standard Pegylated Interferon-Ribavirin Therapy in Treatment-naive & -experienced Patients with Chronic Hepatitis C Infection

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Abstract: Background and study aim: Hepatitis C virus (HCV) is a major cause of liver diseases including chronic hepatitis, liver cirrhosis and hepatocellular carcinoma. Egypt has the highest worldwide prevalence of HCV with more than 90% of HCV isolates are genotype 4 variants. To avoid progression of the disease and its complications, antiviral treatment is needed**.** Genotype-1 infected patients achieved a SVR ranging from 41-52% after 48 weeks of peginterferon-ribavirin with slight higher rates in genotype 4. This study was designed to evaluate the efficacy and safety of adding sofosbuvir to this standard combination therapy in naive patients with chronic hepatitis c and those previously experienced. **Patients and methods**: Ninety patients with chronic hepatitis c were included in this study. Forty five patients were treatment- naïve while the other 45 patients was failed previous course of pegylated IFN and ribavirin. All patients were evaluated by history, clinical examination, imaging and laboratory investigations. Sofosbuvir was added to the standard combination therapy. Side effects during therapy were observed in patients of both groups to assess safety. Real time quantitative PCR was repeated after 12 weeks from the end of treatment to evaluate sustained virological response (SVR) of patients in both groups to assess efficacy. **Results**: The overall SVR in all patients was 72.2%. It was achieved in (35/45) patients in the treatment-naïve group (77.8%) while in the experienced one, it was achieved in (30/45) patients (66.7%) with non-significant difference between both groups (p=0.239). In the treatment-experienced group, patients with breakthrough on old regimen (27/45) patients achieved SVR in a significantly lower rate than those in patients with history of relapse (51.9% vs 88.9 % respectively) (p=0.010). The main side effects developed were headache (84.4 & 55.6%), fever (64.4 & 51.1%), bone aches (57.8 & 40%) and asthenia (53.3 & 37.8%) in naïve and experienced groups respectively. headache was significantly more frequent in the treatment-naïve group (p=0.003). **Conclusion**: Adding sofosbuvir to standard combination therapy (peginterferon-ribavirin) is associated with increased SVR in both treatment-naïve and those experienced with high safety profile in both groups.

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1. Introduction

As many as 170 million persons are chronically infected with the hepatitis C virus (HCV) worldwide and more than 350000 die annually from liver diseases caused by HCV **[1]**. Egypt has the highest worldwide prevalence of HCV with more than 90% of HCV isolates are genotype 4 variants **[2]**. To avoid progression of the disease and its complications, antiviral treatment is needed **[3]**. The goal of treatment is the achievement of SVR in which circulating HCV RNA is undetectable 12 weeks after the treatment with the use of a highly sensitive assay **[4]**.

Until 2011, the combination of pegylated interferon (Peg IFN) and ribavirin for 24 or 48 weeks was the approved treatment for chronic hepatitis C **[5]**. With this regimen, patients infected with HCV genotype 1 had SVR rates of approximately 40% in North America and 50% in Western Europe. Higher SVR rates were achieved in patients infected with HCV genotypes 4 **[6].** The emergence of a new and novel treatment for chronic hepatitis C signals a major change in standard of care **[4].** Three new HCV direct acting antiviral (DAA) drugs were licensed as part of combination therapies for HCV infection. Sofosbuvir, a pangenotypic nucleotide analogue inhibitor of HCV RNA- polymerase is licensed in December 2013, Simeprevir, a second-wave, first generation NS3-4A protease inhibitor active against genotypes 1 and 4 was approved in May 2014 and Daclatasvir, a pangenotypic NS5A inhibitor, was approved in August 2014 **[7].** Each of these three DAAs can be used as a component of a triple combination regimen with Peg

IFN-a and ribavirin, yielding SVR rates of 60– 100% according to the DAA used, the HCV genotype, the presence of detectable pre-existing amino acid substitutions conferring resistance to the DAA used and the severity of liver disease **[8]**. A regimen of 400 mg of sofosbuvir plus peginterferon-ribavirin for 12 or 24 weeks resulted in rates of SVR of 87 to 92% in previously untreated patients with HCV genotype 1 infection **[1]**. Patient with genotype 4 or 6 infection also had higher rates of SVR with similar regimen **[9].**

2. Patients and Methods

Patients

This study was approved by the Ethics and Research Committee of Benha faculty of Medicine, Benha University, Egypt. Data was obtained from ninety patients with chronic liver disease attending or admitted to Kafr El-sheikh Cardiac and Liver Diseases Research Centre during the period from April 2015 to May 2016, divided into two groups: Group (I) included forty five treatment naive patients with chronic HCV infection. Group (II) included forty five patients with chronic HCV infection who failed previous course of (peginterferon-ribavirin) therapy. Informed written consents were taken from all patients before receiving treatment. The following inclusion and exclusion criteria were set by the institute.

Inclusion criteria:

- Positive anti-HCV and HCV RNA with age from 18 to 70 years.
- Child score does not exceed 7 with total serum bilirubin does not exceed 5 mg/dl, Albumin >3.5g/dl, INR <1.2.
- Baseline Hb is not less than 10 g/dl, Platelet count is not less than 100000/mm³, White blood cells (WBC)>4000/mm³, Neutrophil count >2000/mm³.
- Fasting blood sugar 115mg or within 20% of ULN (140mg) and If diabetic HbAIC <8.5%.
- Serum creatinine within normal limit.
- TSH within normal limit.
- ANA<1:160.
- Alpha-Fetoprotein (AFP)<100 ng/ml and If Alpha-Fetoprotein > ULN, C.T is required to exclude malignancy.
- HBsAg negative.
- Female patient practicing adequate contraception and male patient's wife practicing adequate contraception.

Exclusion criteria:

- Child score ≥8.
- Uncontrolled ascites.
- Patients with HCC except after successful curative intervention (3 months after resection or successful loco-regional therapy).
- Exclusion of: co-infection with HBV, autoimmune disease, alcoholic liver disease, hypersensitivity to Interferon or Ribavirin, pregnancy or breast feeding, poorly controlled diabetes, clinically significant retinal abnormalities (by fundus examination), drug-related liver disease, ischemic Cardiovascular disease within the last 6 months (by ECG), patients with organ transplants, substance abuse and severe pre-existing psychiatric condition.

Clinical and laboratory assessment:

All patients in this study were subjected to history taking including age, sex, treatment status (treatment-naïve or -experienced), outcome of previous treatment (break through or relapse), chronic diseases (hypertension, diabetes mellitus, etc), special habits as alcohol intake. Complete clinical examination and laboratory investigations were done including CBC, fasting blood sugar, AST, ALT, serum bilirubin, serum albumin, INR, serum creatinine, HBs Ag, AFP, ANA, TSH, pregnancy test (if ladies in child-bearing period) and PCR for HCV-RNA (quantitative). Fundus examination and radiological examination including abdominal ultrasound were performed for all patients. ECG was done for men over 40 years old andwomen over 50 years old. Liver biopsy was done according to FIB 4 calculation.

During therapy:

CBC and liver function tests were followed to monitor complications. Side effects during therapy were observed. Real time quantitative PCR was done after 4 weeks and at the end of treatment.

After therapy:

PCR was repeated after 12 weeks from the end of treatment to evaluate SVR.

Statistical analysis:

Data was collected and standard sheet was developed. Organization, tabulation, presentation and analysis of data were performed by using SPSS V21 of IBM, USA (Statistical Package for Social Studies version 21). Numerical data was presented as mean and standard deviation (SD). For parametric quantitative data, Student t-test was used for statistical analysis and for non-parametric data; Mann-Whitney U and Wilcoxon Signed Ranks test were used. Categorical data was presented as number and percentage and the chi-squared test was used for statistical analysis. When the chi-squared test was not appropriate, the Mont Carlo Exact Test was applied. The level of significance was adopted at $p<0.05$.

3. Results:

The demographic features and characteristics of the two patients groups were summarized in Table (1). The naive sample studied included 29males (64.4%) and 16 females (35.6%) with mean age of 48.5±6.6 years old and mean BMI of 28.0±3.7 while

experienced sample studied included 32 males (71.1%) and 13 females (28.9%) with mean age of 48.2±6.4and mean BMI of 27.4±3.8. Naïve and experienced patients showed no statically significant differences in components of complete blood count before receiving treatment except in platelets count that was higher in experienced group. Platelets were 135133.3 ±31077.3 and 171222.2 ± 60361.7 in both groups respectively (P=0.001). Serum transaminases showed no statically significant differences in both groups before receiving treatment. Mean values of ALT were 72.2 ± 35.6 and 77.5 ± 55.4 in naïve and experienced groups respectively (P=0.592). While mean values of AST were 83.3 ± 36.0 and 80.0 ± 49.3 in both groups respectively (P= 0.719). Other laboratory investigations done for both groups before treatment as total bilirubin, INR, serum albumin, serum creatinine, fasting blood sugar, alpha fetoprotein also showed no statically significant differences.

Both groups showed no statically significant differences in mean values of PCR before receiving treatment. Mean values were 1.3×10^6IU and 9.3×10^5 IU in naïve and experienced groups respectively (p=0.388).

Liver biopsy was done before treatment for patients with FIB 4 score between 1.45 & 2.5(24/45 and33/45 for treatment-naïve and –experienced patients respectively). Patients with score more than 2.5 were included without biopsy. This was recommended by HCV treatment protocol suggested by the National Committee for Control of Viral Hepatitis at the time of our study to give priority to patients with advanced fibrosis. The majority of patients showed advanced stages of liver fibrosis (METAVIR score = 3 and 4) with a percent age of 95.8% & 78.8% in naïve and experienced groups respectively (p=0.0674) as shown in **(Table 1).**

Table (1): Baseline characteristics of bothgroups before treatment.

Characteristics	**Naïve (n=45)**	**Experienced (n=45)**	**P value**
	N (%)	**N (%)**	
Gender:			
Male	29(64.4%)	32(71.1%)	0.499
Female	16(35.6%)	13(28.9%)	
Age:			
Mean ±SD	48.5±6.6	48.2±6.4	0.822
Range	32(32-64)	24(36-60)	
BMI:			
Mean ±SD	28.0±3.7	27.4±3.8	0.420
Range	16(19-35)	18.30(21.6-39.9)	
Laboratory investigation before treatment:			
HB	13.4±1.6	13.8±1.6	0.172
WBCs$\times10^3$	5.6 ±1.6	5.9±2.1	0.388
Platelets $\times10^3$	135.1±31.0	171.2±60.3	0.001*
ALT	72.2±35.6	77.5±55.4	0.592
AST	83.3±36.0	80.0±49.3	0.719
Total bilirubin	0.95±0.37	0.95±0.30	0.970
INR	1.1±0.1	1.1±0.1	NA
Serum albumin	4.0±0.5	4.9±6.03	0.299
Serum creatinine	1.4±1.0	1.4±1.0	0.790
FBS	97.7±15.2	97.8±14.3	0.955
Alpha fetoprotein	17.9±18.6	15.0±16.9	0.460
PCR before treatment:	1.3×10^6±151695.3	9.3×10^5±128363.7	0.388
Biopsy (fibrosis stage):			
Early (n=8)	1 4.2	7 21.2	0.0674
Advanced (n=49)	23 95.8	26 78.8	
Total (n=57)	24 100	33 100	

SVR was achieved in 35/45 patients (77.2%) in the naïve group while in the experienced one, it was achieved in 30/45 patients (66.7%) with no statistically significant difference between the two groups (P=0.239) as showed in (table 2).

Table (2): Comparison between Naïve and experienced patients as regards response to treatment

SVR	Naïve (n=45)		Experienced (n=45)		P value
	N	%	N	%	
Responders	35	77.8	30	66.7	0.239
Non responders	10	22.2	15	33.3	

In the experienced group, the relapsersshowed significantly better SVR than those with breakthrough (88.9 % Vs 51.9 % respectively) (P=0.01) as shown in (table 3).

Table (3): SVR in relapsers and breakthrough patients in group **II**

Response to treatment	Experienced group of patients (N=45)		P value
	Breakthrough (n=27)	Relapsers (n=18)	
	N (%)	N (%)	
SVR	14 (51.9)	16 (88.9)	0.010*
Non SVR	13 (48.1)	2 (11.1)	

The most common side effects detected were headache (84.4% Vs55.6%), fever (64.4% Vs51.1%), bony aches (57.8% Vs40%) and asthenia (53.3% and 37.8%) in the treatment naïve and experienced groups respectively. Headache was significantly higher in treatment naïve group (P=0.003)**.**

Table (4): Comparison between Naïve and experienced patients as regards side effects

Side effects	**Naïve (n=45)**		**Experienced (n=45)**		**P value**
	N	**%**	**N**	**%**	
Headache	38	84.4	25	55.6	0.003*
Fever	29	64.4	23	51.1	0.200
Bony ache	26	57.8	18	40	0.092
Asthenia	24	53.3	17	37.8	0.138
Anorexia	4	8.9	4	8.9	NA
Hair loss	4	8.9	7	15.6	0.334
Vomiting	3	6.7	5	11.1	0.459

Pancytopenia appeared to be the most prominent noticed side effect on this regimen with significant p value in both groups. Also serum transaminases significantly declined in both groups after treatment as shown in **(Table 5).** However there was no statically significant difference between the two groups (**Table 6).**

Table (5): Effect of treatment on blood component and liver enzymes in both groups

Variables		**Naïve (n=45)**		**P value**
		Before treatment	**After treatment**	
HB	**Mean ±I SD**	13.43±1.6	11.29±1.58	<0.001*
WBCs×10^3		5.6±1.6	3.8±1.5	<0.001*
PLT×10^3		135.1±31.0	114.2±42.0	0.002*
ALT		72.27±35.6	46.49±34.5	<0.001*
AST		83.38±36.0	52.75±30.1	<0.001*
Variables		**Experienced (n=45)**		**P value**
		Before treatment	**After treatment**	
HB	**Mean ±I SD**	13.89±1.6	11.5±1.4	<0.001*
WBCs×10^3		5.9±2.1	4.4±1.9	<0.001*
PLT×10^3		171.2±60.3	152.3±49.6	0.059
ALT		77.56±55.4	47.84±40.6	0.001*
AST		80.09±49.3	45.00±26.7	<0.001*

Table (6): Comparison between effect of therapy on blood components and serum transaminases in both groups.

Variables		**After treatment**		**P value**
		Naïve (n=45)	**Experienced (n=45)**	
HB	**Mean ±I SD**	11.29±1.58	11.5±1.4	0.314
WBCs×10^3		3.8±1.5	4.4±1.9	0.118
PLT×10^3		114.2±42.0	152.3±49.6	<0.001*
ALT		46.49±34.5	47.84±40.6	0.865
AST		52.75±30.1	45.00±26.7	0237

4. Discussion

Chronic hepatitis C (CHC) is a major health concern worldwide with the highest prevalence in Egypt. Although often clinically silent, it is histologically an insidiously progressive disease leading to liver fibrosis, cirrhosis and HCC **[11].** Therapeutic management of chronic HCV patients traditionally depended on combination of peg-interferon with ribavirin but this regimen showed many serious side effects beside its non-satisfactory efficacy. A second generation of DAAs gave a promising results including sofosbuvir **[10]**. In this study, we investigated the add-on therapy of sofosbuvir to the classic standard therapy of peg-interferon and ribavirin in 90 Egyptian patients including 45 treatment-naïve and an equal number of experienced patients. These patients were chosen according to the protocol of National Committee for Control of Viral Hepatitis.

As regards to response to treatment, the overall SVR in all patients in our study was 72.2%. This result is lower than that reported by the NEUTRINO trial (single-group, open-label study of sofosbuvir plus pegylated interferon –ribavirin for 12 weeks in 327 patients infected with HCV genotyoe1,4,5 and 6 at 56 canters in USA) by **Lawitz et al (2013)** that found that global SVR after 12 weeks of treatment with sofosbuvir plus peg interferon and ribavirin was 91% in naïve patients (90% in genotype 1, 96% in genotype 4 and 100% in genotype 5 and 6) **[12]**. The lower response rate in our study maybe attributed to the high percentage of patients with advanced fibrosis and those with liver cirrhosis, a factor that has been associated with reduced response to treatment. The cause of high numbers of cirrhotic patients in our study was that the Egyptian HCV treatment protocol suggested by the National Committee for Control of Viral Hepatitis at the Egyptian Ministry of Health at the time of our study were concerned to give priority to patients having advanced fibrosis so that they may be protected from hepatic decompensation at the near future. On the other hand, the percentage of cirrhotic patients in the NEUTRINO trial was only about 17%, **[12]**.

Results of our study wereclose to what stated by **Velosa et al (2014**) that found that SVR in patients with cirrhosis was about 80% **[13]**.

Our study showed that SVR is better in the treatment naïve group than experienced one but the difference did not reach the level of significance (p = 0.239). SVR was achieved in 35/45 patients (77.2%) in the treatment naïve group while in the experienced one, it was achieved in 30/45 patients (66.7%) **(Table 2).**

In our study, the experienced group of patients showed that the relapsers showed a significantly higher SVR than of patients with history of breakthrough (p = 0.01). Relapsers (18/45 patients) achieved SVR in a percentage of 88.9 % while patients with breakthrough on old regimen (27/45 patients) achieved SVR in a percentage of 51.9% **(Table 3).**

This was in agreement with **Wehmeyer et al (2015**) that found in his study on 24 patients (11 treatment naïve and 13 experienced patients) with genotype 4 that received sofosbuvir plus peg-interferon and ribavirin that SVR was 100%in the treatment naïve group (11/11) while in experienced group it was 69.2% divided as 33% in break through group (2/6) patients and 100% in relapsers (7/7) patients **[14]**.

The results were in agreement also with **Njei et al (2014**) that concluded from six trials involving 636 patients who received sofosbuvir plus ribavirin for 12 weeks that the outcome was better for treatment naïve patients compared to treatment experienced patients with genotype 1. But patients with genotype 2 and 3 showed similar 12-week SVR for both treatment naïve and experienced patients **[15]**.

Also forty patients with HCV genotype 4 infection in one study by **Buti et al (2017)** have received simeprevir plus sofosbuvir for 12 weeks (73% were males,68% were treatment experienced and 18% were with compensated cirrhosis) and the results were 100% SVR in both treatment naïve and treatment experienced groups **[16]**.

The main side effects on this regimen were headache (84.4% vs.55.6%) in the treatment naïve and experienced groups respectively with significant p value (0.003). Other common side effects were fever (64.4% vs.51.1%), bony aches (57.8% vs.40%) and athenia (53.3% vs.37.8%) in the treatment naïve and experienced groups respectively without significant p value in all**.** Other side effects were hair loss, vomiting, anorexia and irritability as shown in **(table 4).**

This was in agreement with **Lawitz et al (2013)** that reported that the main side effects of this triple therapy were fatigue (59%), headache (36%), nausea (34%) and insomnia (25%). It is noticed that these side effects are similar to those of the old regemin (peg interferon and ribavirin). In this study done by **lawtiz et al (2013)**, patients receiving sofosbuvir plus peginterferon and ribavirin had adverse events that were similar in both type and severity to those seen in patients receiving placebo plus peg interferon and ribavirin. The most common events were fatigue, headache, nausea, and chills and all are well known side effects of interferon. No additional or new adverse events attributable to sofosbuvir were detected **[12]**.

Pancytopenia appeared to be the most prominent noticed side effect in laboratory follow up on this regimen in both groups. This study shows the strong correlation between receiving this triple therapy and decrease of mean values of components of blood picture. These results can be explained by effect of IFN on bone marrow as reported by **Manns et al., (2006) [17].** This was in agreement also with **Fried et al., (2002)** that found that ribavirin causes a dosage-dependent hemolytic anemia and that interferon can suppress bone marrow production of red blood cells **[18]**. **Lawitz et al (2013)** reported that suppression of neutrophils and haemoglobin was substantially greater in patients receiving interferon than in those receiving only sofosbuvir or sofosbuvir and ribavirin **[12]**. This was in agreement with **Wehmeyer et al (2015**) that found in one small study on 24 patients with genotype 4 received the triple therapy that pancytopenia occurred in about 20% as side effect **[14].**

So sofosbuvir is well tolerated, without any additional adverse effects beyond those associated to interferon and ribavirin **[13].** Furthermore, it is expected that these side effects have decreased in frequency on this triple therapy for 12 weeks. This may be due to shorter duration of therapy from 48 to 12 weeks adding on sofosbuvir.

Conclusion:

Adding on sofosbuvir to standard combination therapy (peginterferon-ribavirin) has a reasonable efficacy in both treatment-naive and –experienced patients with chronic hepatitis C. Additionally, this regimen is also well tolerated in both groups.

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