Efficacy and Adverse Effects of Sofosbuvir-Based Therapies (Double and Triple Regimens) in Chronic HCV Patients

Nahla E. Elgammal, Hosam M. Dawod, Amal A. Jouda
Tropical Medicine Department, Faculty of Medicine ,Zagazig University,Egypt

Corresponding Author
Nahla E. Elgammal

Mobile:00201227854032

E mail: nahla.elgammal@yahoo.com

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Background and study aim: Egypt has the highest prevalence of hepatitis C virus in the world and it is about14.7 %. Until 2012, the combination of pegylated interferon-α and ribavirin was the standard of care in CHC. Sofosbuvir has an excellent tolerability and safety. Most severe adverse effects were observed when sofosbuvir was combined with ribavirin and/or pegylated interferon. The aim of this study is to compare double therapy (sofosbuvir + ribavirin) and triple therapy (sofosbuvir + ribavirin +peg- INF) for chronic HCV infection in Egyptian patients as regards efficacy and adverse effects.

Patients and Methods: The study included 72 patients allocated in two groups according to the criteria of eligibility to interferon therapy in the National Committee for Control of Viral Hepatitis protocol. Group I received the double therapy for 24 weeks (ribavirin and sofosbuvir) and group II received the triple therapy for 12 weeks (INF, ribavirin and sofosbuvir). The two groups were followed up all through the period of treatment and for three months after treatment and the all the changes in the laboratory parameters were monitored along with the adverse effects and response to treatment.

Results: The rate of sustained virological response was 88.9% in group I vs 94.4% in group II there was no significant differences between the two groups as regards the side effects encountered during treatment except for fatigue and flu like symptoms which were significantly higher in group II.

Conclusion: Double therapy (sofosbuvir and ribavirin) for 24 weeks is effective as triple therapy (INF, sofosbuvir and ribavirin) for 12 weeks in treating Egyptian patients with hepatitis C with less side effects.

INTRODUCTION

Hepatitis C virus (HCV) is a significant public health problem and the leading cause of liver transplantation and hepatocellular carcinoma **[1]**. A recent systematic review estimated that number of persons infected with HCV diagnosed by presence of anti-HCV antibody and those who are chronically infected diagnosed by HCV RNA decreased from 185 and 150 million persons respectively in 2013 to 150 and 80 million persons respectively in 2014 **[2,3]**.

Egypt has the highest number of hepatitis C virus (HCV) cases globally it is about14.7 % and over 90% of the infections have been reported to be HCV genotype 4 **[4,5]**.

Until 2012, the combination of pegylated interferon-α (peg IFN) and ribavirin (RBV) was the standard of care (SOC) in chronic HCV with a sustained virological response (SVR) in approximately 40-50% of genotype 1 patients after 48 weeks of therapy and 70-80% for genotype 2 and 3 patients after 24 weeks of therapy **[6]**. Sofosbuvir is a nucleotide analogue NS5B polymerase inhibitor approved by the Food and Drug Administration on December 6, 2013, for the treatment of chronic HCV infection as a component of antiviral treatment regimen; it shows high antiviral activity against all HCV genotypes and a high barrier to resistance **[7]**. Sofosbuvir has an excellent tolerability and safety. Most severe adverse effects were observed when sofosbuvir was combined with ribavirin and/or pegylated interferon. In the clinical trials of sofosbuvir, the percentage of

chronic HCV cases who stopped treatment due to adverse effects was 4% in placebo groups, 1% in sofosbuvir plus ribavirin groups and 2% in sofosbuvir plus pegylated interferon and ribavirin groups **[8]**.

This study aimed to compare double therapy (sofosbuvir + ribavirin) for 24 weeks and triple therapy (sofosbuvir + ribavirin +peg- INF) for 12 weeks for chronic HCV infection in Egyptian patients as regards efficacy and adverse effects.

PATIENTS AND METHODS

This study was conducted in Tropical Medicine Department, Zagazig University Hospitals in the period between August 2015 and April 2016. Seventy two patients were included.

Inclusion criteria:
Patients with chronic hepatitis C virus infection diagnosed with positive PCR, without cirrhosis or with compensated cirrhosis diagnosed by combination of clinical, laboratory and radiological parameters

Exclusion criteria:
1. Direct serum bilirubin >2 mg/dl.
2. Serum albumin <2.8 gm. /dl.
3. INR ≥1.7.
4. Platelet count<50000/mm³
5. Ascites or history of ascites.
6. Hepatic encephalopathy or history of hepatic encephalopathy.
7. HCC except 4 weeks after intervention aiming at cure with no evidence of activity by dynamic imaging (CT or MRI) and extra hepatic malignancy.
8. Serum creatinine >2.5 mg/dl.
9. Age below 18 years or over 70 years.
10. Pregnancy or inability to use effective contraceptive.

Criteria for INF eligibility according National Committee for Control of Viral Hepatitis (NCCVH) protocol:
1. Age: 18-60 years old.
2. Total bilirubin ≤1.2 mg/dl.
3. Albumin ≥3.5 gm. /dl.
4. INR ≤1.2.
5. Hemoglobin ≥13 gm/dl in males and 12 gm/dl in females.
6. Total leucocytic count ≥ 4000/ mm.
7. Absolute neutrocytic count ≥1500/mm.
8. Platelet count >150.000/mm.
9. Anti-nuclear antibody ≤2 folds.
10. Absence of current autoimmune disease including thyroid disease.
11. Adequately controlled diabetes mellitus HbA1c ≤8.
12. Absence of proliferative retinopathy.
13. Absence of unstable cardiac disease.
14. Non organ transplant cases.
15. Absence of unstable neuro-psychiatric disorders.
16. Absence of history of Peg INF-documented intolerability.
17. Absence of esophageal or/and gastric varices. However, endoscopy is not prerequisite for treatment strategy decision **[9]**.

The patients were divided according to interferon (INF) eligibility criteria from NCCVH protocol update on May 2015 into two groups :
Group I: Included 36 patients receiving (sofosbuvir + ribavirin) for 24 weeks.
- Ribavirin (weight based: 1200 mg if >75 kg or 1000 mg if <75 kg of body weight) orally.
- Sofosbuvir 400 mg/ day orally.

Group II: Include 36 Patients receiving (sofosbuvir + ribavirin +peg- INF) for 12 weeks.
- Ribavirin (weight based: 1200 mg if >75 kg or 1000 mg if <75 kg of body weight) orally.
- Sofosbuvir 400 mg/ day orally.
- Pegylated interferon alfa-2a (180 ug SC / week) or -2b (bodyweight-adapted). Basically received by INF-eligible patients.

Patients received sofosbuvir under the commercial name *GRATISOVIR* produced by European Egyptian Pharmaceutical Industries Amriya, Alexandria, Egypt, for Pharco Pharmaceuticals. Ribavirin was introduced as *Hepavirin* by Amriya Pharmaceutical Industries and interferon as PegIntron from Schering-Plough.

All the studied patients were subjected to:
- History taking
- Thorough clinical examination
- Investigations including: Laboratory tests: Complete blood picture , Liver profile: Serum bilirubin, SGOT, SGPT, ALP, total protein and Serum albumin, Kidney profile: Serum creatinine, Blood Urea, Uric acid, Coagulation profile: PT and INR, Viral markers: HBsAg, HCV IgG, Alpha-feto protein, Autoimmune markers (ANA), Thyroid stimulating hormone, Blood sugar and Glycosylated hemoglobin A1c for diabetics, HCV PCR using the COBAS® TaqMan® HCV Test v2.0.
- Abdominal ultra-Sonography (U/S): Sonoscape S11 machine with a transducer of 3.5 MHz was used to detect: Surface modularity, Overall coarse

and heterogeneous echo texture, Segmental hypertrophy/atrophy, Caudate width: right lobe width >0.65, Reduction of the transverse diameter (<30 mm) of the medial segment of the left lobe (segment IV) (Lafortune et al., 1998), Signs of portal hypertension: Increased portal vein diameter: >13 mm, Portal vein thrombosis, Portosystemic collaterals, Splenomegaly, Ascites. [10,11]

Follow up:

Patients were followed up throughout treatment by clinical evaluation, CBC, liver function after 1 week of treatment then every month till end of treatment and PCR for HCV RNA after 4 weeks, End of Treatment (EOTR) and 3 months after stoppage of therapy for triple therapy group and after 4 weeks, 12 weeks, EOTR and 3 months after stoppage of therapy for double therapy group.

- The primary efficacy end point was the percentage of patients in each group with SVR 12, defined as HCV RNA <15 IU/mL 12 weeks after stoppage of treatment.
- Treatment was expected to be stopped for patients with the following criteria : HCV RNA ≥ the lower limit of quantification (LLOQ) after 2 consecutive HCV RNA < LLOQ, Confirmed HCV RNA >1 log 10 increase from nadir, HCV RNA ≥ LLOQ through 8 weeks of treatment, Severe bacterial infection or serious adverse events.
- Patients in the two groups were followed up monthly during treatment and for 3 months after end of treatment for any developed adverse effects with complete analysis including onset, course, duration, association, frequency, if the patient asked for medical advice, took any medications and if had been admitted to hospital for these side effects.
- Grading of these adverse effects was done according to the common terminology criteria of adverse events 2010 as follows: **[12]**
  - **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention.
  - **Grade 2** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Life (ADL).
  - **Grade 3** Severe or medically significant but not immediately life-threatening; hospitalization; limiting self-care.
  - **Grade 4** Life-threatening consequences; urgent intervention needed.
  - **Grade 5** Death related to adverse effect.

Statistical analysis:

Data were checked, entered and analyzed using SPSS version 19 EPI-INFO 6 and for data processing and statistic. Numerical data were expressed as mean and standard deviation and the comparison between numerical data is done with t test. We used number and percentage to express qualitative data and chi-square test to compare them.

RESULTS

Table (1) shows that there was no significant difference between the two groups as regards demographic data. When we compared the baseline laboratory parameters of the two patients groups we found significant differences as regards platelets count, bilirubin, albumin and liver enzymes serum levels as shown in table (2),while there was no significant differences between the two groups in the hemoglobin concentration, WBC's count, PCR, percentage of cirrhotic patients or percentage of splenomegally. There was no significant difference between the two groups in the virological response all through the period of treatment as seen in table (3).

The comparing of the two groups as regards the expected side effects of treatment revealed that there was no significant difference between them, except for fatigue and flu-like symptoms which were encountered more frequently in group II as seen in table (4). Table 5 compares between the two groups as regards the value of the change in their laboratory levels from base time to end of treatment and revealed that the increase in bilirubin level was significantly higher in group II, while significant decline in the level of enzymes ALT and AST in group I when compared to group II.

Table (1): Demographic data and baseline characteristics of studied population

	Group I N = 36		Group II N = 36		t	P value
Age (years)						
X±SD	45.3±7.6		44.2±10.0		0.52	0.6
Range	33-59		24-60			
Gender	**No**	**%**	**No**	**%**	**X^2**	**P-value**
Male	20	55.6	25	69.4	1.48	0.2
Female	16	44.4	11	30.6		

*P value ≤ 0.05 is significant

Table (2): Baseline laboratory and sonographic data of studied population

Mean ± SD	Group I N=36	Group II N=36	t	P value
Hemoglobin (gm/dl)	13.95±0.9	13.7±1.1	0.92	0.35
Platelet (10^3/mm^3)	112.4 ± 18.9	226.8±55	11.7	0.001*
White blood count (10^3/mm^3)	6 ± 1.5	6.6 ± 1.7	1.6	0.102
Biliubin (mg/dl)	1.5±0.2	0.7±0.2	19.1	0.001*
Albumin (gm/dl)	3.1 ± 0.2	4.3±0.3	17.1	0.001*
AST (IU/L)	67.2 ± 33.3	36.2±21.1	4.7	0.001*
ALT (IU/L)	51.6 ± 34.5	32.7±32.9	5.37	0.02*
PCR (IU/L)	1012794.1±125241.9	999632.17±1254289.805	0.045	0.965
Cirrhosis	6(16.7%)	5(13.9%)	X^2 0.11	0.74
No cirrhosis	30(83.3%)	31(86.1%)		
Splenomegally	6(16.7%)	5(13.9%)	0.11	0.74

*P value ≤0.05 is significant. PCR: Polymerase Chain Reaction. AST: Aspartate Aminotransferase. ALT: Alanine aminotransferase

Table (3): Comparison between the two groups as regards rate of virological response to treatment

	Group I N=36		Group II N=36		X^2	P
	No	**%**	**No**	**%**		
4 week -ve PCR	36	100.0	36	100.0	0.0	1.0
EOTR-ve PCR	36	100.0	36	100.0	0.0	1.0
SVR 12	32	88.9	34	94.4	0.18	0.66

*P value ≤0.05 is significant. PCR: Polymerase chain reaction – SVR 12: sustained virologic response 12 weeks after stoppage of treatment - EOTR: end of treatment response

Table (4): Comparison between the two groups as regards frequency of side effects

	Group I N=36		Group II N=36		X^2	P value
	No	%	No	%		
Fever	2	5.6	6	16.7	1.27	0.26
Chills	2	5.6	6	16.7	1.27	0.26
Flu like	1	2.8	7	19.4	4.99	0.02*
Bone pain	4	11.1	5	13.9	0.0	1.0
Fatigue	10	27.8	21	58.3	6.85	0.008*
Nausea	12	33.3	12	33.3	0.0	1.0
Constipation	12	33.3	12	33.3	0.0	1.0
Diarrhea	4	11.1	4	11.1	0.0	1.0
Pruritus	7	19.4	6	16.7	0.09	0.75
Headache	8	22.2	12	33.3	1.11	0.29
Insomnia	7	19.4	9	25.0	0.32	0.57
Anemia <10 gm/dl	8	22.2	8	22.2	0.0	1.0
Platelet <50 X 10^3/mm^3	0	0.0	0	0.0	0.0	0
WBC<3 X10^3/mm3	0	0.0	0	0.0	0.0	0
Any Adverse effect	36	100	36	100	0.0	1.0
Serious Adverse effect	0	0.0	0	0.0	0.0	0
Adverse effect leading to discontinuation of treatment	0	0.0	0	0.0	0.0	0

*P value ≤0.05 is significant

Table (5): Comparison between the two groups as regards the value of the change in laboratory parameters over the treatment duration

Mean ± SD	Group I N= 36	Group II N=36	t	P value
Change in Hemoglobin (gm/dl)	1.5 ± 1.7	1.8 ± 1.4	0.8173	0.41
Change in PLT (10^3/$mm^{3)}$	20.1 ± 15.8	21.7 ± 58	0.8736	0.15
Change in WBC (10^3/$mm^{3)}$	1.9 ± 1.5	2 ± 2.4	0.8327	0.21
Change in Bilirubin (mg/dl)	0.1 ± 0.7	0.3 ± 0.5	2.0925	0.04*
Change inAlbumin (gm/dl)	0.1 ± 0.3	0.1 ± 0.4	0.1982	0.848
Change in AST (IU/L)	33.1 ± 29.2	5.3 ± 22.7	4.5099	0.0001*
Change in ALT (IU/L)	21.1 ± 29.3	0.8 ± 20.6	3.4006	0.0011*

*P value ≤0.05 is significant

DISCUSSION

Egypt has the highest burden of liver disease due to HCV worldwide. There was in 2013 about 770,000 cirrhosis cases, 16,000 HCV-related hepatocellular carcinoma and 33,000 HCV related liver mortalities **[13,14]**. The 2015 Egyptian Health Issue Survey estimated that 3.7 million cases of HCV viremiain Egypt in 2015 **[15]**.

By the time this study was started in August 2015, there was only two regimens of treatment available in Egypt and approved by the National Committee for Control of Viral Hepatitis (NCCVH), the INF-based regimen (Sofosbuvir, pegylated interferon and Ribavirin) for three months for patients who were eligible for interferon therapy and INF-free regimen (Sofosbuvir and Ribavirin) for six months and (Sofosbuvir and simeprevir) for 3 months for patients who were INF-ineligible **[9]**. In November 2015 the NCCVH protocol was updated to add new regimens in HCV treatment including daclatasvir *(Daklinza®)* in combination with sofosbuvir with or without ribavirin, ledipasvir in single tablet with sofosbuvir *(Harvoni®)* with or without ribavirin and Paritaprevir-r/ombitasvir with or without ribavirin **[16]**.

This work is aimed to compare the two regimens, double regimen (sofosbuvir + ribavirin) and triple regimen (sofosbuvir + ribavirin +peg- INF) for treatment of chronic HCV infection in Egyptian patients as regards adverse effects (laboratory

and clinical adverse effects) and efficacy (SVR and enzymatic response).

In current study, a significant difference was present between the two groups as regards baseline platelet count and serum albumin levels which were higher in triple therapy group, while the liver enzymes and bilirubin were higher in double therapy group, this difference in baseline data is explained by that the patients were not randomly selected but each patient was allocated to certain treatment group according to the NCCVH criteria for INF eligibility.

As regards virological response in this study, both regimens resulted in rapid suppression of HCV-RNA by week 4 in all patients (100%) with HCV-RNA <15 IU/ml. At the end of treatment, 100% of patients received triple or dual therapy had a HCV-RNA <15 IU/ml. This agrees with the results of Doss et al. **[17]** who noticed that by week four of therapy with sofosbuvir and ribavirin, all patients had HCV RNA less than the lower limit of quantification (LLOQ), and all of them had maintained virological suppression while receiving therapy. Also, these results were near to the results of NEUTRINO study, which was a single-group study of sofosbuvir plus peg interferon–ribavirin and by week 4, the percentage of patients with rapid and substantial decreases in serum HCV RNA levels was 99% **[18]** while, Ruane et al. **[19]** found that the HCV RNA levels declined rapidly from 5.97 log10 IU/ml to1.74 log10 IU/ml after only one week from starting treatment with sofosbuvir and ribavirin, all those results confirm rapidity, potency and value of sofosbuvir addition to treatment regimens.

The primary efficacy end point is a sustained virological response, which is HCV RNA level below the lower limit of quantification, at 12 weeks after the end of treatment (SVR12). In this study, 94% (34/36) of patients received triple therapy achieved SVR, while 89% (32/36) of patients received dual therapy achieved SVR. These results are nearly similar to the NEUTRINO study in which 295 of the 327 patients (90%) on triple therapy had a sustained virologic response 12 weeks after treatment **[18]** while, Wehmyer et al. **[20]**, studied the efficacy and safety of sofosbuvir-based triple therapy and reported a higher SVR 12 response rate (100%) in HCV genotype 4.Doss et al. **[17]** study reported a SVR12in 90% (46/51) and 77% (40/52) for 24 weeks and 12 weeks of sofosbuvir and ribavirin therapy respectively, suggesting the interferon-free regimen of sofosbuvir and ribavirin for either 12 or 24 weeks is successful in treating treatment-naïve and treatment-experienced Egyptian patients with genotype 4 HCV and emphasizing on its efficacy.

All patients had suffered from adverse effects during treatment and most adverse effects were of grade 1 severity according to the CTCAE grading. Adverse effects were mild without intervention or affection of Activities of Daily Living (ADL) **[12]**. The reported adverse effects included constitutional adverse effects as fever, chills, flu-like symptoms, bone pain and fatigue however, no serious adverse effects were detected or any patient had stopped the treatment, this can be explained in part by the relatively short treatment duration in relation to the previous 48 weeks and on other hand, the safety of sofosbuvir and the close follow up.

Significant difference was present between the two groups as regards fatigue and flu like symptoms which were higher in triple therapy group than double therapy group. These results agree with the study of Ruane et al. **[19]** in which the most common adverse events were headache, insomnia and fatigue with no patient stopped treatment due to an adverse event.

In the studied groups, a Hemoglobin level <10 g/dL occurred in 22% of patients which is mostly due to hemolysis, a well-known adverse effect of ribavirin combination treatment with onset of hemolysis is usually after 2 to 3 weeks of therapy and it is a dose dependent, this could explain the same incidence rate of hemoglobin decrease below 10gm/dl although different duration of treatment in the 2 groups. On the other hand, thrombocytopenia $<50 \times 10^3/mm^3$ and leucopenia $<3 \times 10^3/mm^3$ were not reported in our study.

Multiple laboratory abnormalities had been encountered during follow up. Both groups showed reduction in hemoglobin, platelet count, WBC's count at end of treatment (EOTR) but the value of this reduction was not significantly different in both groups. This means that the hematological changes were nearly the same in both groups. This disagrees with Christensen et al. **[21]** who reported that reduction in the hemoglobin level is expected with ribavirin and reductions in the neutrophil count are expected with peg interferon, so patients with triple therapy are more liable to hematological disturbances than patients with double therapy. This can be explained by that the short duration of therapy (3 months in triple therapy group) had a role in these results.

In our study, a comparison between the two groups as regards the value of the change in their laboratory levels from base time to end of treatment revealed a significant change in bilirubin level in group II in comparison to the group I, although, it is a very mild increase in front of minimal decrease in group I .On the other hand, a significant change (decrease) in the level of enzymes (ALT and AST) in group I when compared to group II. This is probably due to longer treatment duration in group I (6 months) allowing for improving and normalization of bilirubin and liver enzymes.

CONCLUSION

Interferon-free regimen of sofosbuvir and ribavirin for 24 weeks is as successful in treatment of Egyptian patients with chronic HCV as the interferon-based triple therapy in association with sofosbuvir and ribavirin for 12 weeks and with higher tolerability and less side effects.

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Conflicts of interest: None.
Ethical approval: The protocol of the study was approved by the ethical committee of Faculty of Medicine, Zagazig University. Informed consents were obtained from all patients.

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