Efficacy of Sofosbuvir Plus Ribavirin with and without Pegylated Interferon in Management of Egyptian Chronic Hepatitis C Patients

Magdy Al Dahshan[1], Samy Zaky[2], Sameh Mohamed Seif El-Din[3], Mohammed Salah Ali[1], Alaa Nouh[4] , Radi Hammad[3]

[1]*Internal Medicine Department, Al-Azhar University, Cairo, Egypt*
[2]*Tropical Medicine Department, Al-Azhar University, Damita, Egypt*
[3]*Internal Medicine Department, National Hepatology and Tropical Medicine Research Institute, Cairo, Egypt*
[4]*Tropical Medicine Department, Menoufia University, Menoufia, Egypt*

Corresponding Author
Radi Hammad

Mobile:
00201224778267

E mail:
dr_radyhammad@hotmail.com

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Background and study aim: Egypt is one of the highest prevalence of antibodies to hepatitis C virus (HCV) in the world, estimated nationally at 6.3%. Applying best treatment protocol has a great impact on the national disease burden. DAAs open the door to decrease HCV prevalence as well as to treat infected subjects.

Patients and Methods: In this study 1000 patients treated by Pegylated interferon, Sofosbuvir and weight adjusted Ribavirin. Another group of 1000 patients treated by Sofosbuvir and weight adjusted Ribavirin.

Results: Two groups showed sustained virological response : 90.1% and 72.3% respectively. Both groups approved that previous treatment status and viral load has no impact on response prediction. Both showed that males are more likely to respond than females.

Conclusion: Addition of Direct Acting Antivirals (DAAs), like sofosbovir, to the standard treatment with interferon and ribavirin improved the duration of the treatment and the sustained virological response (SVR). Treating of cirrhotics by PEGINF+SOF+RBV and SOF+RBV leads to decrease success rates. Validation of SVR once will be a golden rule.

INTRODUCTION

The World Health Organization has declared hepatitis C a global health problem, with approximately 3% of the world's population (roughly 170-200 million people) infected with HCV. In the US, approximately 3 million people are chronically infected, many of whom are still undiagnosed. In Egypt the situation is quite worse. **[1]**

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

The goal of antiviral therapy is to cure hepatitis C via a sustained elimination of the virus. Importantly, long-term benefits of sustained virological response (SVR) are the reduction of HCV-related hepatocellular carcinoma and overall mortality. **[3]**

The development of pegylated interferon α (PEG-IFN) improved the pharmacokinetics of IFN, allowing more convenient dosing intervals and resulting in higher SVR. **[4]** In HCV G4, the most prevalent in Egypt. Sustained virological response in Egyptian patients treated with PEG-IFN alfa-2a and ribavirin was estimated to be around 60%. **[5]**

The standard treatment of the HCV was PEG IFN+RBV. The preliminary results indicated that 51% of patients (most with HCV genotype 4, which causes approximately 90% of HCV infections in Egypt) achieved a sustained virological response **[6]**

The development of direct-acting antiviral agents (DAAs) against HCV

has revolutionized the treatment of chronic hepatitis C. In 2011, the first selective protease inhibitors (PI) were approved for patients with HCV Genotype1. Boceprevir (Victrelis®) and telaprevir (Incivek®; Incivo®) improve SVR rates by up to 75% in naïve HCV Genotype1 patients. **[7] & [8]**

On December 6, 2013, FDA approved SOVALDI (sofosbuvir) tablets for the treatment of chronic hepatitis C (CHC) infection as a component of a combination 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. **[9]**

Treatment with interferon is associated with troublesome side effects, including influenza-like symptoms, depression, fatigue, and cytopenias, and requires weekly subcutaneous injections. A substantial proportion of patients with HCV infection are either unable or unwilling to receive an interferon based regimen. **[10]**

A pilot study evaluated the INF-free combination of SOF+RBV for 12 weeks in HCV-G4 patients of Egyptian ancestry showing 79% SVR12 in Naïve and 59%in experienced patients. **[11]**

This study aims to evaluate the efficacy of Sofosbuvir plus Ribavirin with or without pegylated interferon in management of Egyptian chronic hepatitis C patients.

PATIENTS AND METHODS

It is a retrospective cross-sectional study conducted on chronic hepatitis C Egyptian patients with fibrosis score F3 and F4 who attended to National Hepatology and Tropical Medicine Research Institute, Cairo, Egypt to receive anti-HCV therapy.

Patients divided into 2 groups :

Group I: (1000) IFN-eligible persons received daily sofosbuvir (400 mg) and daily weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG INF for 12 weeks.

Group II: (1000) IFN-ineligible/ IFN-unwilling persons received daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks.

RESULTS

Group I: Age is ranged between 19 and 60 years old (mean 50 ± 7 years), Males represent 52.9% of the group and females represent 47.1% of the group, 24.9% of patient was diabetics, Naïve patients represent 72.1% of the group and experienced patients represent 27.9% of the group.

End of treatment response was 99.7% while SVR-wk12 &24 was the same as shown in table below

Table (1): End of treatment response in group I

	Frequency	Percent	Valid Percent	Cumulative Percent
Negative	901	90.1	90.1	90.1
Positive	99	9.9	9.9	100
Total	1000	100.0	100	

Actually percentage of negative PCR are exactly the same for weeks 16, 24, 36 (weeks 4, 12, 24 after end of treatment) respectively.

In Group I; Viral load or previous treatment experience didn't has any significant relation with treatment response. But Males were more likely to respond than female significantly. In addition to the age which show significant relationship to response.

Table (2): Relations to treatment response in group I

Factor	Odds ratio	Confidence interval	p-value	Comment
Naive Vs. treatment experienced	1.18	0.69 – 1.99	0.527	No significant difference
Gender	1.78	1.01 – 2.99	0.026	Significant association shows that males were 1.8 times more likely to have response to the treatment therapy than females
Factor	**Df**	**Independent t-test**	**P-value**	**Comment**
Age in years	718	3.1	0.002	There was a significant difference in age between those who responded to the therapy and those who did not respond
Viral load before starting the therapy	718	-0.78	0.433	No significant difference

Group 2: Age is ranged between 20 and 60 years old (mean 52 ± 6 years), Males represent 61.9% of the group and females represent 38.1% of the group, 32.5% of patient was diabetics, Naïve patients represent 73.5% of the group and experienced patients represent 26.5% of the group.

End of treatment response was 99.9% while SVR-wk12 &24 was the same as shown in table below

Table (3): End of treatment response in group II

	Frequency	Percent	Valid Percent	Cumulative Percent
Negative	723	72.3	72.3	72.3
Positive	277	27.7	27.7	100
Total	1000	100.0	100	

Actually percentage of negative PCR are exactly the same for weeks 28, 36, 48 (weeks 4, 12, 24 after end of treatment) respectively.

In Group 2; Viral load, age or previous treatment experience didn't has any significant relation with treatment response. But Males were more likely to respond than female significantly.

Table(4): Relations to treatment response in group II

Factor	Odds ratio	Confidence interval	p-value	Comment
Naive Vs. treatment experienced	1.53	1.01-2.32	0.05	No significant difference
Gender	3.37	2.16 – 5.37	<0.001	Significant association shows that males were 3 times more likely to have response to the treatment therapy than females
Factor	**Df**	**Independent t-test**	**P-value**	**Comment**
Age in years	539	1.33	0.183	No significant difference
Viral load before starting the therapy	539	0.21	0.834	No significant difference

DISCUSSION

SVR in this study, for patient received triple therapy, is less than Lawitz's trial **[13]** as it was 96% but in this study it was only 90.1%, and it could be due to many reasons ;the large number in our study (1000 patients in comparison to 28 patients in Lawitz's trial).In our study we selected the patients with fibrosis stage (F3, F4) only (according to NCCVH protocol) in comparison to Lawitz's trial that didn't assess the degree of fibrosis. Our study included naïve and experienced patients, in comparison to Lawitz's trial included only naïve patients.

SVR in this study, for patient received double therapy, is less than Esmat's trial **[12]** as it was 90% but in our study it was only 72.3% and it could be due to many reasons ;the large number in our study (1000 patients in comparison to 51 patients in Esmat's trial).In our study we selected the patients with fibrosis stage (F3, F4) only (according to NCCVH protocol) in comparison to Esmat's trial that 23% of subjects were cirrhotics .Our study included 73.5% naïve patients and 26.5% treatment experienced patients, in comparison to Esmat's trial included 14% naïve patients and 63% treatment experienced.

Conclusion: Addition of Direct Acting Antivirals (DAAs), like sofosbovir, to the treatment with interferon and ribavirin improved the duration of the treatment and the sustained virological response (SVR). Treating of cirrhotic by PEGINF+SOF+RBV or SOF+RBV leads to increase success rates. Validation of SVR once will be a golden rule.

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