

Effect of Sofosbuvir, Brand Drug (Sovaldi) Versus Generic (MPI Viropack) in Treating Chronic HCV Genotype 4 Infection among Egyptian Patients

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Abstract

Sofosbuvir is a NS5B polymerase inhibitor with effective pan-genotypic coverage and approved for use in genotype IV. With the availability of both the brand drug (Sovaldi- Gilead) and the generic form (MPI-Viropack- Marcyrl Pharmaceutical Industries, Egypt) in Egypt, we conducted this comparative study to evaluate and compare the safety and efficacy of both forms. We recruited 105 treatment naïve patients with chronic HCV infection. For all of them the following was done: Liver and kidney function tests, CBS, ECG, fundus examination, Abdominal ultrasound, Fibro scan, HBsAg and HCV RNA by Quantitative PCR. They were divided into three well matched groups, 35 patients each. The first group received triple therapy, Peg Interferon (Peg Intron- MSD), Ribavirin in a weight adjusted dosage and Sovaldi- Gilead 400 mg once daily. For the second group, the same treatment as in group I but MPI viropack 400 mg once daily instead of Sovaldi. For the third group, dual therapy was given using Ribavirin in a weight adjusted dosage and either Sovaldi 400 mg once daily (17 patients) or MPI viropack once daily (18 patients). Follow – up was done during treatment at week 4 and 12 and post-treatment at 4, 12, 24 weeks using liver and kidney function tests, CBC and HCV RNA by quantitative PCR.

SVR12 was detected in 32 (91.4%) patients in group I, II and in 24 (68%) patients in group III. SVR24 was detected in 31(88.6%) patients in group I and II, 21(60%) in group III. The side effects were comparable in group I and II in the form of nausea and abdominal discomfort.

From this study, we found that both the brand and the generic forms of Sofosbuvir in combination with PegINF/R proved safe and effective in Egyptian patients with chronic HCV – genotype 4 infection, with comparable safety and efficacy profile. However, patients received only Sofosbuvir with Ribavirin combination, in spite of safety and efficacy, the high relapse rate (40%) may limit future use of this regimen.

Keywords: HCV treatment; Generic drugs; HCV Genotype4; Egyptian patients with HCV

Introduction

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide [1,3,4] and Egypt has the highest prevalence in the world. The number of chronically infected persons worldwide is estimated to be about 180 million, but most are unaware of their infection [5,6,7].

HCV anti-viral therapy has undergone a revolution, moving very rapidly from IFN-based therapies with cure rates of 40–70% depending on genotype, to the advent of direct-acting anti-viral drugs achieving cure rates in excess of 90% for all genotypes with treatment duration reduced to as little as 8 weeks [9,10,13,14]. The validity of measuring HCV RNA 12 weeks after completion of treatment (SVR12) has been evaluated and approved by regulators in the USA and Europe, as an equivalent end point [19].

The currently available direct-acting anti-viral drugs are split into three classes defined by their HCV target protein: the protease inhibitors targeted against the NS3/4a protease; and the NS5a complex inhibitors and polymerase inhibitors, which are directed against the NS5b protein. This latter class can be further divided into nucleotide and non-nucleotide inhibitors [9,14].

In the last few years, numerous directly acting antiviral agents (DAAs) have been implemented successfully in treatment algorithms of chronic hepatitis C virus infection. As combination therapy with PEGylated interferon (PEGIFN) α , ribavirin, and / or other DAAs, potent DAA-based regimens result in HCV eradication in the vast majority of patients with chronic hepatitis C [2,9,14].

Sofosbuvir (SOF) (Sovaldi[®]) is the first available once-daily NS5B polymerase inhibitor with pan-genotypic coverage approved 12/2013 by FDA and 1/2014 by EMA and approved for use in genotype IV (AASLD 2014, EASL 2015). For genotype 1, PEGIFN/ RBV + SOF for just 12 weeks leads to 89% SVR in treatment-naïve patients [20,21,22].

Treatment of HCV genotype 4 infection: Six treatment options are available in 2015 for patients infected with HCV genotype 4, including 2 IFN-containing regimens and 4 IFN-free regimens. In settings where none of these options is available, the combination of PegIFN- α and ribavirin remains acceptable (EASL 2015).

Patients infected with HCV genotype 4 can be treated with a combination of weekly PegIFN- α , daily weight based ribavirin (1000 or 1200 mg in patients < 75 kg or \geq 75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks (B1) [14,18-23].

However, the costs of Sovaldi- Gilead was too high to be adopted for treatment in spite of the company reduced price for the Egyptian patients [8,11,12]. With the introduction of new generic drugs for Sofosbuvir to the Egyptian drug market having the same bio-equivalence to the brand drug, we put a study plan to compare the safety and efficacy of the brand drug (Sovaldi- Gilead) versus the firstly introduced generic drug (MPI-Viropack- Marcyrl Pharmaceutical Industries in Egypt) and follow up was done up to 24 weeks' post-treatment.

Patients and Methods

In this study we recruited 105 treatment naïve patients with chronic HCV infection from Sept. 2014 to April 2015. After having their written consent, the following was done for all of them: Liver function tests (S. bilirubin, ALT, AST, S. Albumin, PT and PC), CBS, Blood urea and creatinine, ECG, fundus examination, Abdominal ultrasound, Fibro scan, HBsAg and HCV RNA by Quantitative PCR. The patients were divided into three well matched groups, 35 patients each. According to Fibro scan, in the first group, 23 patients had F2, 9 patients F3 and 3 patients F4 and the second group showed F2 in 22 patients, F3 in 10 patients and F4 in 3 patients, and the third group showed 22 patients with F2, 6 patients with F3 and 7 patients with F4.

For the first group, triple therapy was used, Peg Interferon (Peg Intron- MSD according to body weight), Ribavirin in a weight adjusted dosage and Sovaldi- Gilead 400 mg once daily.

For the second group, triple therapy was also used, Peg Interferon and Ribavirin as in group I and MPI viropack 400 mg once daily.

For the third group, dual therapy was given using Ribavirin in a weight adjusted dosage and either Sovaldi 400 mg once daily (17 patients) or MPI viropack once daily (18 patients).

Follow - up was done during treatment at week 4 and 12 and post-treatment at 4, 12, 24 weeks using liver and kidney function tests, CBC and HCV RNA by quantitative PCR.

Results

The demographic and clinical data were similar in all groups with asthenia as the main presenting symptom in 97 (92%) patients and tender hepatomegaly in 78 (74%) patients as the main sign. Liver enzymes were elevated in all patients. ECG and fundus examination were normal in all patients. Kidney and synthetic liver functions were normal. HBsAg was negative in all patients. Basal HCV RNA by RT PCT range was 350X10³ to 9.0X10⁶. At week 4 during treatment, there was normalization of liver enzymes in 34 (97%) patients in all

groups. CBC showed mild decrease in HB level (1-2 gm/dl) in 18, 19, 15 patients in group I, II, III respectively. HCV RNA was not detected in 34 (97%) patients in group I, II and III. At week 12 during treatment, there was normalization of liver enzymes in 34 (97%) patients group I and II, and 33 patients (94%) in group III. CBC showed mild decrease in HB level in 18, 19, 15 patients in group I, II, III respectively. HCV RNA was not detected in 34 (97%) patients in group I, II and 33(94%) patients in group III.

At week 4 post-treatment, there was normalization of liver enzymes in 34 (97%) patients group I and II, and in 24 patients (68%) in the third group. HCV RNA was not detected in 34 (97%) patients in group I, II and 24 (68%) patients in group III.

At week 12 post treatment, there was normalization of liver enzymes in 33 (94%) patients group I and II, and 21 patients (60%) in the third group. As regards to SVR24, HCV RNA was not detected in 31 (88.6%) patients in group I, II and in 21 (60%) patients in group III.

Group	Group I No (%)	Group II No (%)	Group III No (%)
(-) ve PCR			
At week 4 of treatment	34 (97%)	34(97%)	34(97%)
At week 12 of treatment	34(97%)	34(97%)	33 (94%)
SVR4	34(97%)	34(97%)	24 (68%)
SVR12	32(91.4%)	31(88.6%)	21(60%)
SVR24	31(88.6%)	31(88.6%)	21(60%)

Table 1: HCV PRC response in the three groups.

The relapse in group III was detected in 14 patients equally distributed between Sovaldi and MRI viropack groups. There was no correlation between the response or relapse rate and the viral titer throughout the period of the study. Fibro scan showed different degrees of fibrosis ranged from F2 to F4 and was comparable in the three groups.

Group	Group I No (%)	Group II No (%)	Group III No (%)
Fibrosan Grade			
F0	0	0	0
F1	0	0	0
F2	23 (65.7%)	22 (62.9%)	22 (62.9%)
F3	9 (25.7%)	10 (28.6%)	7 (20%)
F4	3 (8.6%)	3 (8.9%)	6 (17.1%)

Table 2: Fibrosan Grading in the three groups.

Patients with F0 and F1 were excluded as the policy of Egyptian National Hepatitis program at its beginning was to treat HCV patients with significant fibrosis. All the relapsed patients had significant grade of fibrosis in group I and II (4 patients), and in group III, there was 14 relapses (6 had F2, 3 had F3 and 5 had F4).

The side effects were comparable in group I and II: Nausea and abdominal Pain in 20 (57%) patients in Gr. I versus 21 (60%) in Gr. II, diarrhea in 3 (8.5%) patients in Gr. I versus 4 (11.4%) patients in Gr. II, headache in 4 (11.4%) patients in both groups. However, in Group

III the side effects were mild including asthenia in 20 (57%) patients and mild gastric upset in 15 (43%) patients disregarding the type of Sofosbuvir used (Table 4).

Discussion

HCV is a worldwide infection affecting about 180 million persons with the highest prevalence in Egypt [1,2,3,4,5,6,7]. The standard of care therapy depended upon the combination of Peg Interferon with weight adjusted Ribavirin for 24-48 week in genotype IV, with limited success rate (SVR24 45-55%) and many side effects [19]. With the introduction of DAAs in 2011 by Telaprevir [15] and Bociprevir [16], the situation started to change in the form of higher response rate and lower relapse rate. However, this treatment was genotype specific and large bill burden [16]. With the introduction of Sofosbuvir in 2013, as NS5B polymerase inhibitor with pan genotypic activity, single oral dose and high efficacy with limited side effects, HCV treatment started to change [2,9,18]. EASL in 2015 issued 6 guidelines for HCV treatment genotype IV and the first recommendation was to use PegIFN/Ribavirin with Sofosbuvir for 12 weeks [21,22,23]. Based on this recommendation and with the availability of both the brand form – Sovaldi (Gilead) and the first generic drug MRI Viropak (Marcyrl Pharmaceutical Industries, Egypt) and due to economic reasons [8,11,12], we conducted this study to compare the safety and efficacy of both regimens. The study included 105 naïve patients with chronic HCV infection. They were divided into 3 comparable and matching groups each having 35 patients. For all groups full clinical, biochemical, virological and radiological assessment was done. They were given the standard of care therapy plus Sovaldi in group I, with MRI Viropack in group II and only Sovaldi or MRI Viropack in group III and were followed for 24 weeks. Biochemically, there was anemia in all groups that was attributable to the use and dose of Ribavirin [24,25,26]. There was no hepatic or renal function deterioration as mentioned in other studies [18, 21]. As Regards to the virological assessment, there was a good response in all groups during the first 4 weeks of treatment approaching 97%. However, there was relapse in 3 patients (8.3%) in group I and II, and in 14 patents (40%) in group III at 24 weeks follow-up (Table 2). Fibro scan [17] showed different degrees of fibrosis ranged from F2 to F4 and was comparable in the three groups (Table 2). All the relapsed patients had significant grade of fibrosis in all groups.

Relapses	Group 1 No (%)	Group II No (%)	Group III No (%)
Fibrosan Grade			
F2	0	1 (2.9%)	6 (17.1%)
F3	1 (2.9%)	1 (2.9%)	3 (8.6%)
F4	3 (8.6%)	2 (5.7%)	5 (14.3%)

Table 3: Relation between Fibrosan grade and relapses.

The side effects of therapy were comparable in the three groups in the form of asthenia, headache, abdominal and epigastric discomfort (Table 4) and these side effects were comparable to other previous similar studies [24,25].

	Group I No (%)	Group II No (%)	Group III No (%)
Side effects			
Nausea	20 (57%)	21 (60%)	15 (42.9%)
Abdominal pain	20 (57%)	21 (60%)	17 (48.6%)
Diarrhea	3 (8.3%)	4 (11.4%)	4 (11.4%)
Headache	4 (11.4%)	4 (11.4%)	3 (8.3%)
Asthenia	18 (51.4%)	19 (54%)	20 (57%)
Gastric upset	10 (28.6%)	12 (34%)	15 (42.9%)

Table 4: Clinical Side effects of medications in the three groups.

Conclusion

From this study, we found that both the brand and the generic forms of Sofosbuvir in combination with Peg/R proved safe and effective in Egyptian patients with chronic HCV – genotype 4 infection, with comparable safety and efficacy profile. However, the combination of Sofosbuvir (Both brand and generic) with Ribavirin, in spite of safety and initial efficacy, there was a high relapse rate (40%) that may limit the future use of this regimen.

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