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Research Article

Sofosbuvir Plus Daclatasvir with Fixed Versus Weight Adjusted Dose of Ribavirin for Treatment of HCV, Genotype 4 Among Egyptian Patients

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Abstract

HCV infection is a common health problem worldwide and in Egypt. With the recent introduction of DAAs, the treatment modalities have been completely changed. Various DAAs combinations have been suggested. With the availability of the generic forms of both Sofosbuvir and Daclatasvir (MPI-Viropack- Daclavirocyrl, Marcyrl Pharmaceutical Industries in Egypt), we gave the two DAAs with two dosage forms of Ribavirin, one is Ribavirin weight adjusted doses and the other is Ribavirin fixed dose (800 mg /day) for the whole treatment duration (12 weeks). Included in this study 475 patients with chronic HCV infection and were divided into three groups: Group I (193 patients) who received MPIviropack and Daclavirocyrl with weight adjusted dose of Ribavirin, Group II (193 patients) who received MPIviropack and Daclavirocyrl with fixed dose of Ribavirin and Group III (89 patients) n who received only MPIviropack and Dacavirocyrl. The treatment was given for 12 weeks with 12 weeks follow-up to assess SVR12. The treatment was safe and effective in the three groups with overall response of 92%, 95% and 91% in group I, II, III respectively, with more side effects especially HB reduction in group I. We recommend the use of MPIviropack and Daclavirocyrl combination with fixed dose Ribavirin as an effective and safe treatment modality in treating chronic HCV, genotype 4 among Egyptian patients.

Keywords: *HCV in Egypt; HCV with DAAs; HCV Genotype 4; Ribavirin Dosages*

Introduction

Hepatitis C virus (HCV) infection is prevalent in every country where it has been sought making it a global health problem with an estimated prevalence of over 184 million people worldwide [1]. However, the prevalence rates of infection are highly heterogeneous with a disproportionate burden of infection in countries with limited health care resources. In addition to heterogeneity in the prevalence of infection there is also heterogeneity in the distribution of viral genotypes; in most developed countries genotypes 1 and 3 dominate whereas genotypes 4, 5, and 6 are more common in countries with limited healthcare resources [2]. North Africa is recognized as one of the highest prevalence regions for HCV globally with an average 3.6% of adults infected with HCV. However, within this region Egypt stands out as the country with the highest prevalence, recently estimated at 14.7% in subjects aged 15 to 59 years with lower prevalence in urban areas (10.3%) compared with 18% in rural areas [3]. The rapid emergence of the epidemic in Egypt was originally fueled by the mass treatment of schistosomiasis using the injectable drug tartar emetic during the 1960s [4]. As the population who were initially infected have now aged and died, the prevalence rate in Egypt has fallen. Furthermore, there is a profound age cohort effect with much higher prevalence rates in the population over 50 years. Furthermore, the HCV epidemic in Egypt faces significant geographical disparities, the prevalence being highest in the Nile Delta (17.5%) and lower in Cairo, Alexandria, or Suez (9.5%) and 3.8% in Frontier Governates [3]. However, as the morbidity and mortality from HCV infection depend on the duration of infection, the burden of cirrhosis and hepato-

cellular carcinoma (HCC) in Egypt is still rising and is expected to produce more than 200,000 deaths from cirrhosis or HCC over the next decade [5,6]. Over the past 15 years HCV genotype 4 has been regarded as difficult to treat, requiring 48 weeks of pegylated interferon and ribavirin (PegIFN/RBV) and achieving sustained virological response (SVR) rates of only 50%. New IFN-free DAA combinations have significantly improved SVR rates in HCV genotype 4 infected patients. With the advent of all oral direct-acting antiviral drugs with a broad range of genotypic activity and a low incidence of side effects, we are entering an exciting new era on the therapeutics of hepatitis C virus (HCV). As the majority of people infected with HCV live in resource-limited settings it is important to overcome the barriers that restrict access to treatment in these areas. Drug costs, public and professional education, simplified diagnostics, and political imperative all need to be addressed before the majority of HCV-infected individuals can benefit from the new generation of HCV antivirals [4].

The European Commission has approved Daklinza (daclatasvir), on August 27, 2014 a potent, pan-genotypic NS5A replication complex inhibitor for use in combination with other medicinal products across genotypes 1, 2, 3 and 4 for the treatment of chronic hepatitis C virus (HCV) infection in adults [7]. Daklinza, when used in combination with sofosbuvir, is an all-oral, interferon-free regimen that provided cure rates of up to 100% in clinical trials, including patients with advanced liver disease [8-11]. With the availability of generic DAAs drugs in Egypt with proven safety and efficacy as the brand named drugs, the treatment became available for a large sector of Egyptian patients with chronic HCV infection [12].

With the new Interferon, free DAAs regimens for HCV treatment, still Ribavirin is needed in many schedules specially with PI and NS5A Inhibitors. Although the mechanism of its action is not well understood, it is needed to enhance the response rate and decrease the relapse rate in addition to shorting the treatment duration as in patients with cirrhosis. In-spite of Ribavirin inclusion in many treatment strategies, most of the side effects were related to Ribavirin doses [10]. Sofosbuvir and Daclatasvir combination with or with-out Ribavirin proved to be safe and effective in treating HCV genotype 1,3,4 [13]. To evaluate the efficacy and safety of Ribavirin in treating Egyptian patients with chronic HCV genotype 4 infection, and with the availability of the generic forms of both Sofosbuvir and Daclatasvir (MPI-Viropack- Daclavirocyrl, Marcyrl Pharmaceutical Industries in Egypt), we gave the two DAAs with two dosage forms of Ribavirin, one is Ribavirin weight adjusted doses and the other is Ribavirin fixed dose (800 mg /day) for the whole treatment duration (12 weeks).

Patients and Methods

Included in this study 475 Egyptian patients with chronic HCV genotype 4 infection Patients were recruited between January to August 2016. The inclusion criteria were all patients with chronic HCV infection and compensated liver disease including Child grade A cirrhosis, HB level above 12 gm% with written informed consent. The exclusion criteria were patients with HB level below 12 gm%, decompensated cirrhosis (Child grade B and C), pregnant ladies or were not using contraception, concomitant HBV infection or HCC.

After getting their written informed consent, the following was done for all of them: Full clinical assessment, Biochemical tests including liver and kidney profile, CBC, Abd. Ultrasound, Fibroscan, HBsAg, quantitative HCV RNA using RT PCR.

The included patients were divided into 3 groups. In this open study, patients were randomized to be included in group I (193 patients) who received daily dose of MPI Viropack 400 mg with Daclavirocyrl 60 mg and Ribavirin in weight adjusted doses, group II (193 patients) who received daily dose of MPI Viropack 400 mg and Daclavirocyrl 60 mg and Ribavirin given in a fixed daily dose of 800 mg. The third group (89 patients) who served as a control group to received only daily dose of Viropack 400 and Daclavirocyrl 60 without Ribavirin. The treatment duration for the 3 groups was 12 weeks with 12 weeks post-treatment follow-up to assess SVR12.

The treated patients of the three groups were followed-up at the 4^{th} and 12^{th} weeks of treatment and for another 12 weeks post-treatment.

At each visit the following was done: CBC, Liver and kidney profile, abdominal ultrasound and quantitative PCR for HCV using RT-PRC.

In the study cohort, 162 patients (34%) had been previously treated, including 48 patients (10%) who had relapsed on sofosbuvir and Ribavirin only. Fibroscan was done to assess the fibrosis score where score 1 and 2 indicates no cirrhosis, and score of 3 indicates advanced fibrosis and score of 4 indicates compensated cirrhosis. In group I fibrosis score of 1, 2, 3, 4 was detected in 80, 38, 35, 40 patients and in group II, Fibrosis score was of 1, 2, 3, 4 was detected in 78, 42, 31, 42 patients and in group III Fibrosis score of 1, 2, 3, 4 was detected in 25, 22, 19, 23 respectively (Table 1).

Character	Gr. I (No.193)	Gr. II (No. 193)	Gr. III (No 89)
Age, mean	52 +3	53 + 4	55 + 2
Sex, males	110 (57%)	102 (53%)	50 (56%)
Asthenia	159 (82.4%)	160 (82.9%)	60 (67.4%)
Abd. Discomfort	88 (45.6%)	97 (50.3%)	55 (28.5%)
Bleeding tendencies	50 (25.9%)	55 (28.5)	14(7.3%)
Itching	17(8.8%)	19 (9.8%)	4 (4.5%)

Table 1: *Clinical data for the three groups.*

The hepatitis C RNA count ranged from 0.1to 6 million IU/mL.

There were no virologic breakthroughs with the 12-week treatment.

Results

Included in this study 475 patients with chronic HCV infection, out of them 262 were males (55%) with ages ranged from 22 to 66 years with a mean of 44 years (Figure 1 and 2). The main presenting symptoms were athenia, Abdominal pain, bleeding tendency, itching (Table 2).

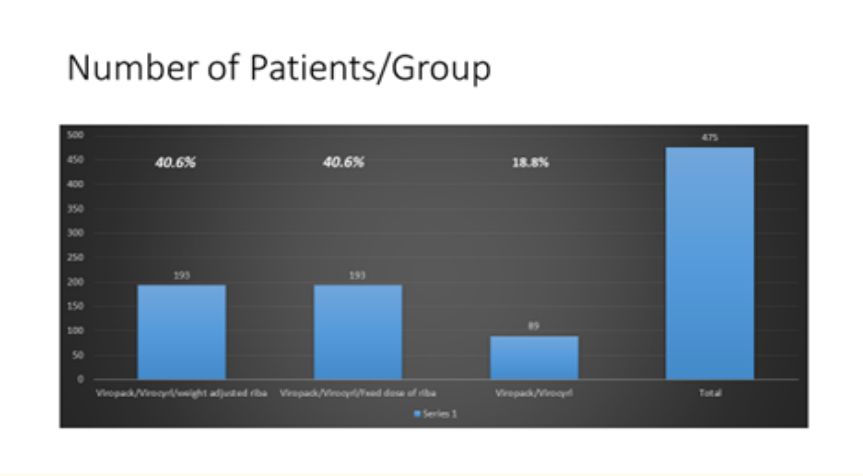
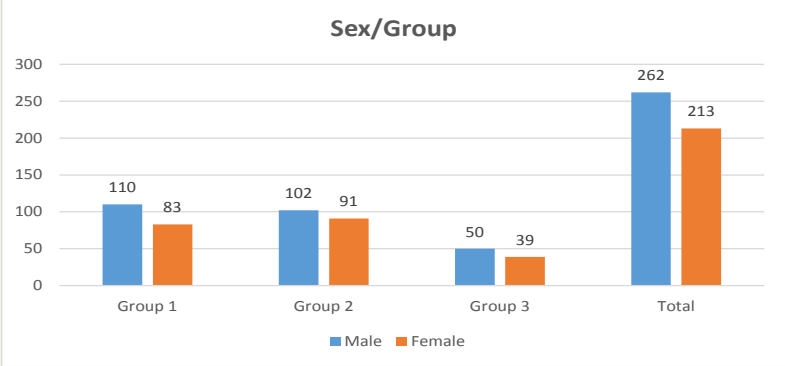


Figure 1: *Patients numbers in each group.*



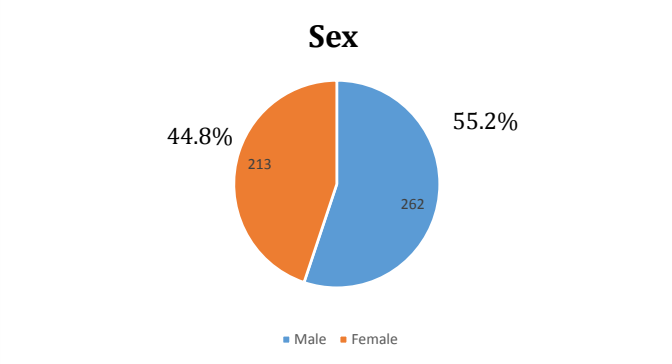


Figure 2: *Male/Female ratio total and in each group.*

Biochemical test	Group I	Group II	Group III
Elevated ALT, AST	157 (81%)	163 (84%)	80 (90%)
CBC:			
HB > 12 gm%	100%	100%	100%
Leucopenia	38 (20%)	39 (20.2%)	24 (27%)
Thrombocytopenia	43 (22.2%)	45 (23.3%)	26 (29.2%)
HCV RNA Level	0.1 - 5 mill/ml	0.1 - 6 m/ml	0.2 - 4.5 m/ml

Table 2: *Biochemical Profile before treatment.*

Their labs. At baseline revealed elevated liver enzymes in 422 patients (89 %), with HB level above 12 gm% in all of them. At the end of 12 weeks treatment, liver enzymes were normalized in 178 (92.2%) in group I and in 180 (93%) % in group II and in 84 (94.3%) in group III. Also, HB level was decreased to a level below 12 gm% in 87 (45%)%, in 25 (13%), in 2 (2.2%) in group I, II, III respectively (Table 3,4). The decreased HB level was more significant in group I who receive Ribavirin in weight adjusted doses. PCR testing by RT-PCR revealed a level ranged from 0.1 to 6 millions before therapy. At 4 weeks of treatment, PCR became (-) ve in 177 (91.7%),178 (92.2%), 80 (90%) in group I, II, III respectively (Table 5- Figure 3). Overall response rate with (-) ve PCR at 12 weeks of treatment was detected in 180 (93.2%), 184 (95.3%), 82 (92%)in group I, II, III respectively (Table 6). SVR12 was detected in 178 (92.2%), 183 (94.8%), 81 (91%) in group I, II, III respectively (Table 7, 8 and 9 Figure 4). In relation to fibrosis score (Figure 5), the response rate ranged from 95 - 100 % in F1, F2 and it decreased to 80 - 93% in F3, F4 (Figure 6). The non-responders were 13 (6.7%), 12 (6.2%), 7 (7.8%) patients in group I, II, III. The

non-responders were 32 (6.7%) patients out of 475 patients. In relation to fibrosis score, 29 out of 32 non-responders were in F3, F4. As regards to relapses, they were 2, 2, 1 in Group I, II, III respectively. Again, the relapses were in F4 patients in the three groups. As regards previously treated patients, (Figure 7) 155 out of 162 patients responded to Sofosbuvir, Daclatasvir combination forvonyl 12 weeks.

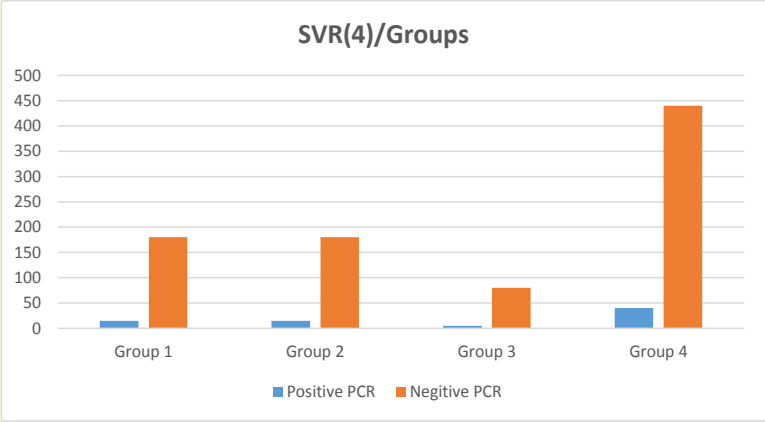


Figure 3: *SVR 4.*

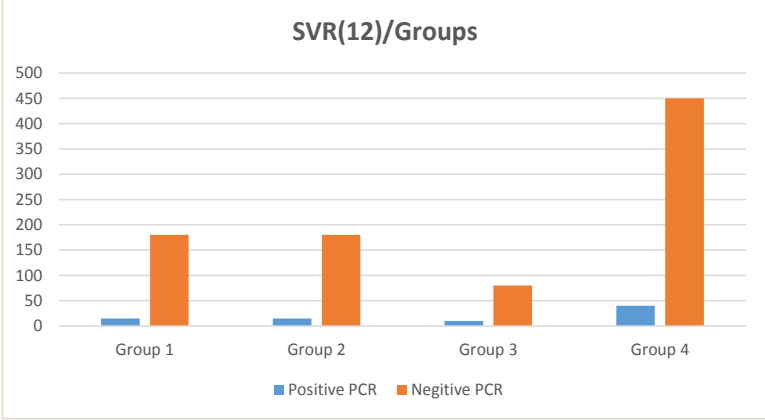


Figure 4: *SVR 12.*

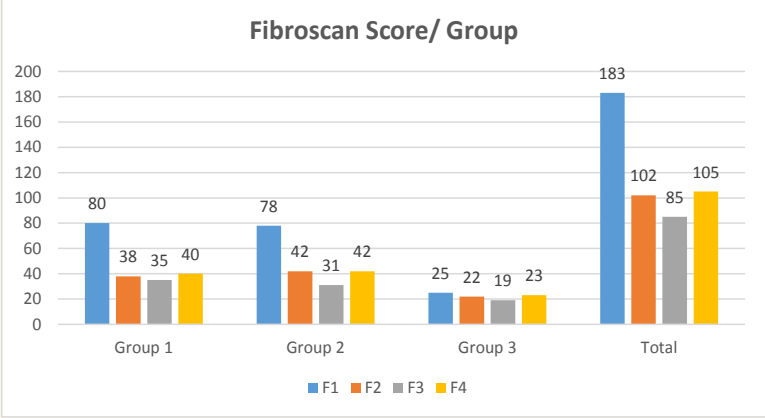


Figure 5: *Fibroscan score in each group.*

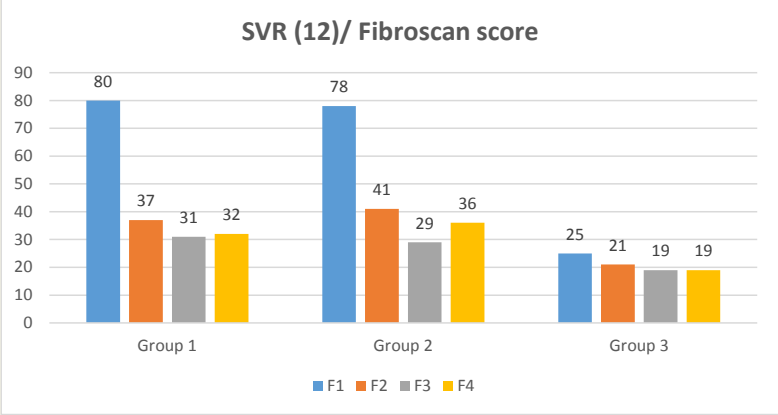


Figure 6: *SVR in relation to Fibroscan Score.*

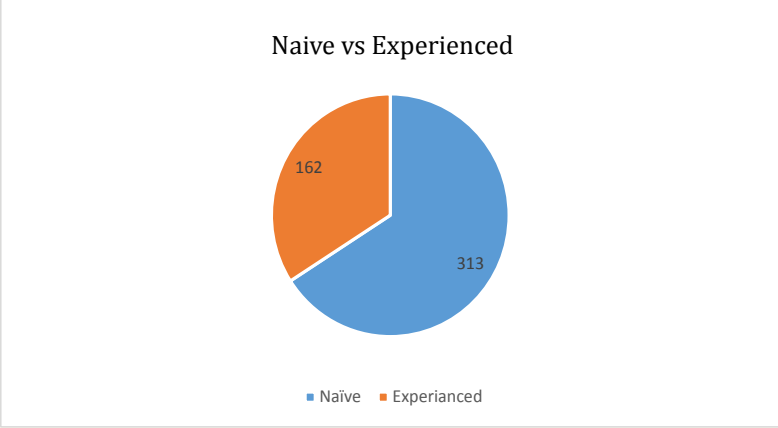


Figure 7: *Naïve versus experienced patients.*

Biochemical test	Group I	Group II	Group III
Elevated ALT, AST	15 (7.7%)	13 (6.7%)	5 (5.6%)
CBC:			
HB < 12 gm%	87 (45%)%	25 (13%)	2 (2.2%)
Leucopenia	41 (21%)	39 (20.2%)	24 (27%)
Thrombocytopenia	45 (23.3%)	45 (23.3%)	26 (29.2%)
HCV RNA (-) ve	180 (93%)	181 (93.8%)	82 (92%)
HCV RNA (+) ve	13 (6.7%)	12 (6.2%)	7 (7.8%)

Table 3: *Biochemical Profile at week 12 of treatment.*

Fibroscan score	Group I (No. 193)	Group II (No.193)	Group III (No. 89)
F1	80 (41%)	78 (40%)	25 (28%)
F2	38 (20%)	42 (22%)	22 (25%)
F3	35 (18%)	31 (16%)	19 (21%)
F4	40 (21%)	42 (22%)	23 (26%)

***Table 4**: Fibroscan results in all groups.*

HCV RNA	Group I	Group II	Group III
(-) ve PRC	177 (91.7%)	178 (92.2%)	80 (89.9%)
(+) ve PCR	16 (8.3%)	15 (7.8)	9 (10.1)

***Table 5:** HCV RNA level at week 4 during treatment.*

HCV RNA	Group I	Group II	Group III
HCV RNA (-) ve	180 (93%)	184 (95%)	82 (92%)
HCV RNA (+) ve	13 (6.7%)	12 (6.2%)	7 (7.8%)

***Table 6:** HCV RNA level at week 12 during treatment.*

Fibrosis score	(-) ve PCR in Gr.I	(-) ve PRC in Gr. II	(-) ve PCR in Gr. III
F1	80 (100%)	78 (100%)	25 (100%)
F2	37 (97%)	41 (97.6)	21 (95%)
F3	31 (88.6%)	29 (93.5%)	17 (89,5%)
F4	32 (80%)	36 (85.7%)	19 (82.6%)
Overall Response	180 (93%)	184 (95%)	82 (92%)

***Table 7:** HCV RNA level at the end of 12 weeks treatment in relation to Fibrosis score.*

Fibrosis score	(-) ve PCR in Gr.I	(-) ve PRC in Gr. II	(-) ve PCR in Gr. III
F1	80 (100%)	78 (100%)	25 (100%)
F2	37 (97%)	41 (97.6%)	21 (95%)
F3	30 (85.7%)	29 (93.5%)	17 (89.5%)
F4	31 (77.5%)	35 (83%)	18 (78%)
Overall Response	178 (92%)	183 (95%)	81 (91%)

***Table 8:** Viraemia level at 12 weeks post- treatment (SVR12) in relation to Fibrosis score.*

Outcome	Sustained Response, n	Virologic Failure	Death. N
Treatment regimen			
- Sof & Dakla, + wt. adjusted dose Ribavirin (n = 193)	178 (92%)	15 (8%)	0
-Sof. &Dakla, + fixed dose Ribavirin (n = 193)	183 (95%)	10 (5.2%)	0
Sof, Dakla only (n = 89)	81 (91%)	8 (9%)	0
- Overall (n = 475)			
Patient Characteristic			
-Cirrhosis (n = 105)	84 (80%)	21 (20%)	0
-Advanced Fibrosis (n = 85)	76 (89.5%)	9 (10.5%)	0
-Previously treated (n = 162)	144 (88.9)	18 (11.1%)	0

Table 9: *Outcomes 12 Weeks After Treatment.*

At the time of failure, all four patients who relapsed had compensated cirrhosis in the 3 groups.

The most common adverse events were athenia, nausea, abdominal pain and headache. Hemoglobin reduction was detected in 45% in group I but none of the patients discontinued treatment because of adverse events (Table 10).

Side Effects	Gr. I No (%)	Gr. II No (%)	Gr. III No (%)
Nausea	86 (44.5%)	82 (42.5%)	41(46%)
Abd. Pain	81(42%)	82 (42.5%)	32 (16.6%)
Diarrhoea	8 (4%)	9 (4.7%)	4 (4.5%)
Headache	34 (16.7%)	31 (16%)	8 (9%)
Insomnia	13 (6.7%)	14 (7.3%)	2 (2.2%)
Asthenia	98 (50.7%)	92 (47.7%)	32 (16.6%)
Gastric upset	32 (16.6%)	31(16%)	11 (12.4%)
HB reduction	87 (45%)	25 (13%)	2 (2.2%)

Table 10: *Adverse effects in the three groups.*

Discussion

HCV is a worldwide infection affecting about 180 million persons with the highest prevalence in Egypt [1-5]. 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 [14]. With the introduction of DAAs in 2011 by Telaprevir [15] and Boceprevir [16], the situation started to change in the form of higher response rate and lower relapse rate. 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 [17-22]. With the FDA approval for Daclatasvir as NS5A inhibitor with pan genotypic activities [7], EASL in 2015 and AASLD 2016 issued many guidelines for HCV treatment genotype IV including the combination of Sofosbuvir and Daclatasvir with or without Ribavirin 12 weeks [23,24]. The mechanism of action of Ribavirin is not well understood, however its use may increase the response rate, decrease the relapse rate or shorten the treatment duration. However, addition of Ribavirin is associated with most side effects noted in

these patients and its side effect was dose dependent [25]. For that reason, we conducted this study to compare the safety and efficacy of adding Ribavirin in weight adjusted doses and in a fixed dose in HCV treatment for group I and II. The treatment efficacy was higher in GrII (95%) than in Gr.I (92%) and this difference could be due side effects of higher doses of Ribavirin that necessitated change in its doses during therapy and this may affect patient compliance and the response to treatment. The side effects, mainly HB reduction, were more in Gr.I (45%)versus Gr. II (13%) and in both groups , the side effects were more than group III (2,2%)that did not receive Ribavirin [25]. However, the response rate was higher in Gr.II (95%) than in gr.III (91%) . Transient elastography is a good modality to assess the fibrosis score and guide treatment [26]. The response rate with correlated with the fibrosis score where it was from 95 - 100% in F1 and F2 and reduced to 80 - 93% in F3 and F4. The non-response and relapse rate was nearly similar in the 3 groups, and it was evident in F3 and F4 groups of patients.

Conclusion

From this study , we confirmed the safety and efficacy of using the combination of generic forms of both Sofosbuvir and Daclatasvir (MPI-Viropack- Daclavirocyrl, Marcyrl Pharmaceutical Industries in Egypt) in treating HCV genotype 4 infection among Egyptian patients with overall response of 92%, 95% and 91% in group I, II and III respectively and the use of Ribavirin in both weight adjusted and fixed doses was equally effective with slight increase in response rate , but with more side effects especially HB reduction in weight adjusted doses. We concluded that the combination of MPIviropack and Daklaviroyrl with fixed dose Ribavirin was safe and effective in treating HCV genotype 4 among Egyptian patients with SVR12 of 95%.

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