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Original Article

Rapid on-treatment response as a predictor in HCV infected naïve Egyptian patients

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A B S T R A C T

Abstract: ***Background and Study Aims:*** Effect of peginterferon and ribavirin treatment on chronic hepatitis C virus infection has been early established. However, predictors of treatment success need more elucidation. The present study is directed to estimate the importance of rapid virological response, and other host and viral factors in naïve Egyptian patients treated with 48 weeks of pegylated interferon and ribavirin.

Patients and Methods: A total of 111 naïve Egyptian patients with chronic hepatitis C genotype 4 were randomly assigned to a treatment regimen consisting of either peginterferon-alpha-2a (180 µg/week) or peginterferon-alpha-2b (1.5 µg/Kg/week) plus oral ribavirin (10.6 mg/Kg/day). This treatment was given for 48 weeks with a 24-week follow-up. The endpoint was sustained virological response.

Results: Overall, sustained virological response was achieved by 85 (70.2%) patients, while 26 (21.5%) patients relapsed. Rapid virological response occurred in 95 patients where 77 (84.6%) of them attained SVR and 14 (15.4%) of them relapsed (***P***<0.001). Concerning host and viral factors, age, gender and pretreatment viral load, they all did not influence the outcome of therapy. On the other hand, higher liver fibrosis stage according to Metavir score (F_3) significantly modified the sustained virological response compared to stage F_1 with an Odds ratio 5.9 (95% confidence interval (CI): 1.1-31.0) and compared to F_2 with an Odds ratio 7.2 (95% confidence interval (CI): 1.3-40.9).

Conclusion: Rapid virological response is an independent factor that influences the sustained virological response. Besides, low pretreatment fibrosis stage is a predictor of sustained virological response.

Key Words: Rapid virological response, sustained virological response, naïve Egyptian patients, HCV, peginterferon, ribavirin.

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1. INTRODUCTION

Hepatitis C is an infectious disease caused by the hepatitis C virus (HCV) and is a major problem throughout the world. There are an estimated 180 million persons chronically infected with HCV globally (Ghany et al., 2009). HCV exhibits high genetic diversity (Smith et al., 2014), its genotyping classification was expanded into 7 genotypes and 67 subtypes (Messina et al., 2015). Egypt has the highest prevalence of HCV infection (12-13%) and interestingly genotype 4 represents over 90% of cases (EMH, 2007; Al Kady et al., 2009). Chronic hepatitis C infection may result in serious sequelae, such as end-stage cirrhosis, hepatocellular carcinoma (HCC), need for liver transplantation, and premature death (Perz et al., 2006). Both the National Institute of Health (NIH) and the American Association for the Study of Liver Disease (AASLD) have reported that the most efficacious treatment for this disease is the combination of weekly subcutaneous injections of long-acting pegylated-interferon (PEG-IFN) alfa and oral daily ribavirin; as such, this regimen represents the current standard of care (Fried et al., 2002).The standard duration of therapy in patients with genotype

4 infection is 48 weeks. This results in an SVR of 40% to 79% (Diago et al., 2004; Kamal et al., 2005).

Early assessment of viral kinetics during treatment accurately predicts response to therapy and provides additional information about how to individualize treatment (Ferenci et al., 2005). Consequently, duration of therapy may be shortened for patients who respond rapidly and extended for those who respond slowly. Shortened courses of treatment may be useful if adverse effects or costs are an issue and are particularly valuable in patients who experience substantial adverse effects that may pose a health risk if treatment is continued. Rapid virological response (RVR), defined as an undetectable serum hepatitis C virus (HCV) RNA level at week 4 of treatment, is emerging as an important milestone in the treatment of patients who have chronic hepatitis C by using of pegylated interferon-Alfa and ribavirin—the current standard of care. It is rapidly becoming a new tool for predicting which patients with hepatitis C have a high likelihood of attaining SVR. In addition, it may identify patients for whom a truncated course of therapy is appropriate (Poordad et al., 2008).

In this study, we aimed to determine the role of RVR on the response to 48 weeks of peginterferon/ ribavirin for HCV-4 naïve Egyptian patients as a primary aim. The secondary aim of the current study was to investigate the factors associated with RVR and SVR in those patients.

2. PATIENTS AND METHODS

2.1. Study design

This is a prospective, observational, non-interventional study.

2.2. Patients

After the ethical committee approval was taken, 129 patients with chronic hepatitis C were selected from the outpatient clinic of Kafr El-Sheikh Liver and Cardiac Center from December 2009 to October 2011. Out of these, 14 patients did not continue the study due to unknown cause or excluded because of having positive HCV PCR at week 12 or 24 after treatment initiation. Also, breakthrough happened in 4 patients at week 48 leaving 111 patients to be followed up 24 weeks after treatment termination.

Inclusion criteria: Eligible subjects were males and females previously untreated Egyptian patients with chronic hepatitis C, aged 18 to 65 years, who (1) were seropositive for HCV antibodies (third-generation, ELISA) and for HCV RNA by a quantitative polymerase chain reaction (RT-PCR) assay (2) had undergone a liver biopsy that was consistent with chronic hepatitis within 1 year before entry; and (3) had a genotype 4 infection(Muriex HCV –serotyping 1-6 assay).

Other eligibility criteria included neutrophil count greater than 1500 mm^{-3}, platelet count greater than 9 x 10^4 mm^{-3}, hemoglobin level greater than 12 g/dl for men and greater than 11 g/dl for women, serum creatinine level less than 1.5 mg/dl, no pregnancy or lactation, and the use of a reliable method of contraception.

Exclusion criteria: on-eligible subjects were patients with hepatitis B surface antigen, human immunodeficiency virus infection, F_0 and F_4 on liver biopsy [according to the scoring system described by Metavir (Ward et al., 2004)], autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, Wilson disease, alpha1-antitrypsin deficiency, decompensate cirrhosis, overt hepatic failure, psychiatric condition, previous liver transplantation, or with evidence of hepatocellular carcinoma (by testing of α-fetoprotein and by ultrasound scanning), poorly controlled diabetes, body mass index >30, abnormal thyroid function, clinically significant retinal abnormalities, alcohol or I.V., drugs abusers and patients with +ve PCR at week 12 or week 24 during the treatment.

2.3. Classification of patients

The studied subjects were classified into two groups according to HCV RNA by PCR at week 4as follows:

- RVR patients: Ninety two patients with negative PCR at week 4 (N=92)
- Non-RVR patients: Twenty six patients with positive PCR at week 4 (N=23)

2.4. Drugs used

After taking written consents from the patients, all of them were treated 48 weeks with either peginterferon alfa-2a (180 µg/week) (Pegasys; Roche, Basel, Switzerland) or peginterferon alfa-2b (1.5 µg/Kg/week) (Pegintron; Schering-Plough, County Cork, Ireland) S.C. in combination with weight-based oral ribavirin (1200 mg/day for patients ≥ 75 Kg, or 1000 mg/day for patients < 75 Kg) (Rebetol; Schering-Plough, Puerto Rico, U.S.A.). HCV RNA titers were assessed prior to treatment and at week 4, 12, 24, 48 (at the end of treatment, EOT) as well as 24 weeks after the end of treatment (week 72).

2.5. Assessment of Efficacy

Rapid virological response (RVR); was defined as PCR-negative serum HCV RNA at week 4 of therapy. Early virological response (EVR); was defined as PCR-negative serum HCV RNA at week 12

of therapy. End-of-treatment virological response was defined as PCR-negative serum HCV RNA at the end of treatment. The endpoint of this study was to assess sustained virological response (SVR); which is defined as HCV RNA PCR-seronegative by the end-of-treatment and throughout the follow-up period. Relapse was defined as HCV RNA reappearance during the follow-up period in patients who achieved an end-of-treatment virological response.

2.6. Evaluation of drug safety

All of the patients were subjected to clinic, weekly during the first month and monthly thereafter along the course of therapy, to check for the appearance of any side effects related to the treatment, and then followed for at least 6 months after discontinuation of treatment to assess for sustained response.

2.7. Statistical analysis

Data were analyzed using IBM SPSS Advanced Statistics version 20.0 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test (or Fisher's exact test) was used to examine the relation between qualitative variables. For quantitative data, comparison between two groups was done using independent sample t-test or Mann-Whitney test. Odds ratio (OR) with 95% confidence interval (CI) were used for estimation of factors affecting SVR. P-value less or equal to 0.05 was considered significant and less than 0.01 was considered highly significant.

3. RESULTS

The epidemiology, clinical, virological and histological characteristics of the 92 RVR patients and the 23 non-RVR patients are shown in Table 1. The two groups of patients were similar according to all baseline characteristics.

Fig 1 reveals that genotype 4 naïve Egyptian patients who showed a RVR at week 4 after treatment with a combination of peginterferon and ribavirin achieved a high SVR (84.6%) and a low relapse rate (15.4%). On the contrary, patients who showed no RVR at week 4 relapsed in 60% while 40% of them cured.

Similarly, Fig 2 shows that the SVR rates differed significantly depending on the fibrosis stage (***P***=0.006), whereas F_1 stage achieved 80.3% SVR and 19.7% relapsed, F_2 achieved 80.5% SVR and 19.5% relapsed and F_3 achieved 33.3% SVR and 66.7% relapsed. Thus, it can be said that the SVR was inversely related to the fibrosis stage while the relapse rate was directly related to it.

Table 2 shows that patients with age ≤45 years did not differ statistically in achieving SVR than patients with age >45 year. According to gender, female and male patients were similar in their response to treatment. On the other hand, as the pretreatment viral load range increased, achieving SVR increased and relapse rate decreased but without any statistical significant difference.

In Table 3, multivariate analysis of RVR and fibrosis stage, the two factors affecting SVR, reveals that RVR is an independent factor affecting SVR with an OR 7.5 (95% CI: 2.5-22.8). F3 stage significantly affects SVR compared to stage F1 with an OR 5.9 (95% CI: 1.1-31.0) and compared to F2 with an OR 7.2 (95% CI: 1.3-40.9).

Side effect Scheme in Table 5 showing that the noted side effects subsided on their own as treatment with peginterferon and ribavirin continued. Oral paracetamol, codeine-containing cough syrup, psychological support, relaxation and bed rest were used to overcome Flu-like symptoms during the first weeks of treatment as shown in Table 4. Hematological side effects that may lead to treatment interruption and then affect the cumulative treatment were almost non-existent.

Table 1. Patient characteristics at the start of the study

Characteristics / Groups	RVR patients (n= 92)	Non-RVR patients (n= 23)	*P* value
Age, years	37.3 ± 11.2	40.4 ± 9.5	0.225
Sex			
Female	23 (76.7%)	7 (23.3%)	0.595
Male	69 (81.2%)	16 (18.8%)	
Weight, Kg	81.1 ± 14.0	82.7 ± 10.1	0.609
Fibrosis Stage			
F_1	53 (57.6%)	10(43.5%)	
F_2	34 (37.0%)	9 (39.1%)	0.132
F_3	5 (5.4%)	4 (17.4%)	
Biochemical data			
ALT, IU/L Median (Range)	40.0 (6.0-181.0)	75.0 (15.4-292.0)	0.059
AST, IU/L Median (Range)	40.0 (7.0-159.0)	55.0 (13.8-264.0)	0.089
Hematological data			
RBCs, ml/cmm	5.04 ± 0.50	5.07 ± 0.48	0.794
WBCs, cell/Cm³	5954.3 ± 1414.3	5649.6 ± 2088.7	0.513
Hb, g/dl	14.1 ± 1.5	14.3 ± 1.5	0.491
Platelets, cell/ Cm³	217± 76	186± 62	0.075

Table 2. Effect of age, sex and baseline viral load on SVR and relapse rate

	SVR patients	Relapse patients	*P* value
Age			
≤ 45 yr (n=85)	65 (76.5%)	20 (23.5%)	0.962
> 45 yr (n=26)	20 (76.9%)	6 (23.1%)	
Sex			
Female (n=29)	22 (75.9%)	7 (24.1%)	0.961
Male (n=82)	63 (76.8%)	19 (23.2%)	
Baseline viral load			
≤ 4 x 10^5 IU/ml (n=82)	63 (76.8%)	19 (23.2%)	
> 4 x 10^5 IU/ml (n=29)	22 (75.9%)	7 (24.1%)	0.916
≤ 6 x 10^5 IU/ml (n=89)	69 (77.5%)	20 (22.5%)	0.634
> 6 x 10^5 IU/ml (n=22)	16 (72.7%)	6 (27.3%)	
			0.379
≤ 8 x 10^5 IU/ml (n=92)	72 (78.3%)	20 (21.7%)	
> 8 x 10^5 IU/ml (n=19)	13 (68.4%)	6 (31.6%)	

SVR, sustained virological response: patients with negative HCV RNA 24 weeks after treatment termination, opposite to "Relapse". Data are expressed as number (%). Statistical analysis was carried out using Chi Square test.

Table 3. Multivariate analysis of RVR and fibrosis stage, the two factors affecting SVR

	R	SD	P value	Odds Ratio (95% CI for OR)
RVR	2.013	0.568	< 0.001**	7.5 (2.5-22.8)
F stage			0.072	
F (F_1 vs. F_3)	1.776	0.847	0.036	5.9 (1.1-31.0)
F (F_2 vs. F_3)	1.975	0.886	0.026	7.2 (1.3-40.9)

R, Regression coefficient. SD, Standard deviation. CI, confidence interval. RVR means patients with undetectable HCV RNA at week 4 after treatment initiation. F_1, F_2, F_3= Fibrosis stage. **Highly significant at $P < 0.01$. Statistical analysis was carried out using Chi square test.

Table 4: Side effects scheme

		Wk1	*Wk2*	*Wk4*	*Wk8*	*Wk12*	*Wk16*	*Wk20*	*Wk24*	*Wk28*	*WK32*	*Wk36*	*Wk40*	*Wk44*	*Wk48*
Flu-like Symptoms	***Fever***	**32**	**17**	**14**	**3**	**1**	**4**	**4**	**3**	**2**	**2**	**2**	**2**	**1**	**0**
	Fatigue	**24**	**20**	**15**	**6**	**3**	**3**	**2**	**4**	**2**	**1**	**0**	**2**	**0**	**0**
	Chills	**8**	**2**	**1**	**3**	**2**	**1**	**3**	**0**	**2**	**1**	**1**	**2**	**0**	**0**
	Myalgia	**11**	**5**	**2**	**2**	**0**	**3**	**2**	**1**	**1**	**1**	**1**	**1**	**0**	**0**
	Arthralgia	**6**	**2**	**2**	**1**	**2**	**3**	**2**	**2**	**2**	**2**	**2**	**1**	**0**	**0**
	Musculoskeletal pain	**6**	**4**	**2**	**2**	**0**	**3**	**4**	**2**	**1**	**1**	**1**	**2**	**0**	**0**
	Headache	**16**	**9**	**9**	**3**	**3**	**5**	**3**	**2**	**4**	**2**	**2**	**2**	**1**	**0**
GIT upset	***Nausea***	**6**	**9**	**3**	**3**	**1**	**2**	**2**	**2**	**2**	**0**	**1**	**1**	**0**	**0**
	Vomiting	**3**	**2**	**4**	**2**	**2**	**1**	**1**	**2**	**2**	**1**	**1**	**1**	**0**	**0**
	Anorexia	**5**	**5**	**4**	**5**	**2**	**3**	**3**	**1**	**2**	**1**	**2**	**1**	**0**	**0**
	Dyspepsia	**3**	**5**	**4**	**1**	**0**	**5**	**2**	**1**	**2**	**0**	**0**	**0**	**0**	**0**
Dermatological symptoms	***Itching***	**7**	**5**	**5**	**6**	**1**	**2**	**1**	**2**	**3**	**0**	**0**	**0**	**0**	**0**
	Skin rash	**2**	**1**	**3**	**2**	**0**	**1**	**1**	**0**	**0**	**0**	**0**	**1**	**0**	**0**
	Hair loss	**3**	**1**	**1**	**0**	**0**	**1**	**1**	**1**	**0**	**0**	**1**	**0**	**0**	**0**
	Injection site reaction	**3**	**2**	**1**	**1**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**0**	**0**
Respiratory symptoms	***Cough***	**4**	**2**	**2**	**3**	**3**	**0**	**2**	**0**	**1**	**0**	**1**	**1**	**0**	**0**
	Shortness of breath	**2**	**0**	**1**	**2**	**1**	**2**	**2**	**1**	**1**	**0**	**0**	**1**	**0**	**0**
Neurological symptoms	***Insomnia***	**0**	**0**	**0**	**2**	**2**	**1**	**1**	**2**	**0**	**0**	**1**	**1**	**0**	**0**
	Depression	**1**	**1**	**0**	**1**	**1**	**2**	**2**	**2**	**2**	**0**	**1**	**0**	**0**	**0**
	Decrease of concentration	**1**	**0**	**0**	**0**	**0**	**1**	**1**	**2**	**1**	**0**	**0**	**0**	**0**	**0**

Fig 1. RVR as a predictor for achieving SVR

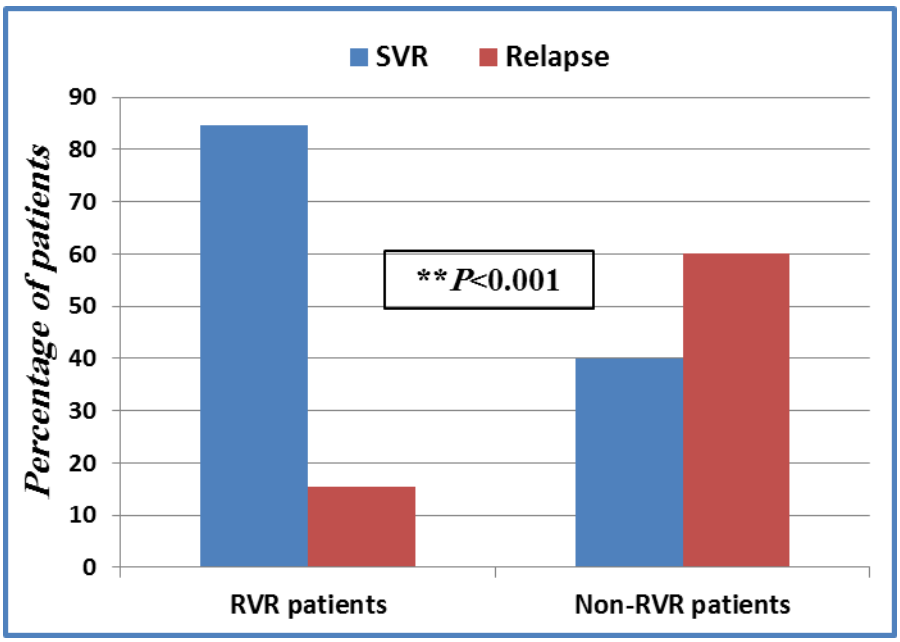

Fig 1. RVR, "Rapid Virological Response": patients with negative HCV RNA at week 4. SVR, "Sustained Virological Response: patients with negative HCV RNA 24 weeks after treatment termination, opposite to "Relapse". ** Highly significant at P<0.001 using Chi Square test.

Fig 2. Fibrosis stage as host predictor for achieving SVR

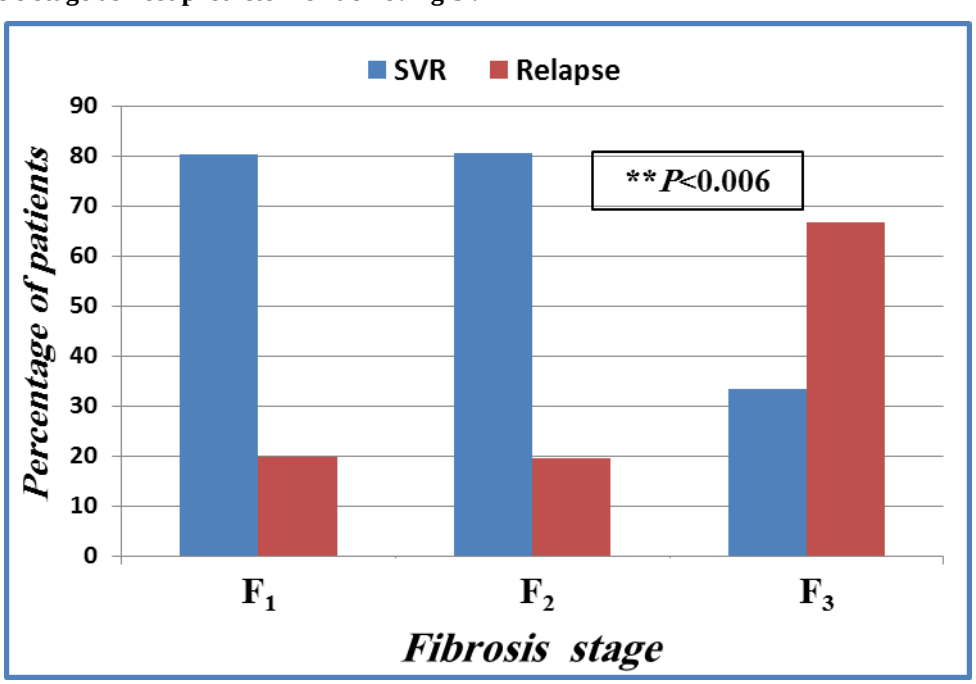

Fig 2. SVR, sustained virological response: patients with negative PCR 24 weeks after treatment termination, opposite to "Relapse". F1, F2, F3= Fibrosis stages ** Highly significant at P=0.006 using Chi Square test.

4. DISCUSSION

In the current study, once treatment has been initiated, the best predictor of cure is the achievement of undetectable serum HCV RNA level at week 4. Whereas, genotype 4 naïve Egyptian patients who showed a RVR at week 4 after treatment with a combination of peginterferon and ribavirin achieved a high SVR (84.6%) and a low relapse rate (15.4%). On the contrary, patients who showed no RVR at week 4 relapsed in 60% while 40% of them cured. This finding is in agreement with those reported by many investigators (Mangia et al., 2005; Yee et al., 2006; Scott and Gretch, 2007; Fried et al., 2008; Shiffman et al., 2008] who showed that rapid virologic response was more important than baseline factors in predicting SVR. Accordingly, some guidelines have discussed shortening therapy in such cases (Mangia et al' 2005; Yee et al' 2006; Ghany et al., 2009; Ferenci, 2012). On the other hand, Ferenci et al (2009) demonstrated in a large randomized controlled trial that extending the duration of treatment with pegylated interferon plus ribavirin reduced the risk of relapse and increased the SVR rate in patients with hard-to-treat HCV genotypes 1 or 4 who did not achieve rapid virological response. In one study (Dimitroulopoulos et al., 2010) done on 30 patients with viral load >8 x 10^5 IU/ml and advanced stage of liver histology, revealed that in Egyptian patients, RVR was the weakest indicator of SVR (11%) and HCV RNA negativity at week 24 presented the best SVR (100%).

Finally, RVR should be viewed not as an isolated parameter, but as one of many treatment components that when used together, can maximize the potential of attaining SVR. Therefore it does not mean that final decisions can be made regarding the overall course of treatment once week 4 is reached. Only, it can be used to motivate patients and has implications for individualization of duration of therapy (Soriano et al., 2007; Ghany et al., 2009).

Concerning the host factors as predictors of response to treatment, it was believed that age is one of the factors that can be used to predict a relatively better or worse than average chance of achieving a SVR. In the current study, no definite relation between the age and treatment failure in naïve Egyptian patients treated with the combination of pegylated interferon and ribavirin was found. This is in agreement with the finding in different studies which revealed that age was not a significant predictor of SVR (Elefsiniotis et al., 2008; Cuenca et al., 2010; Hansen et al., 2011; Khalil et al., 2012). On the other hand, other investigators showed that younger age may be a significant predictor of SVR (Kamal et al., 2005; Al Ashgar et al., 2009; Reddy et al., 2009; Al-Saeed, 2011). In conclusion, age may only represent the duration of infection not the date and mechanism of infection.

Concerning the viral factors as predictors of response to treatment, low baseline viral load has been shown to be an independent predictor of SVR, regardless of genotype in numerous studies (Manns et al., 2001; Berg et al., 2006; Jacobson et al., 2007). With respect to the suggestions that baseline of $\leq 4 \times 10^5$ IU/ml is the most effective cut-off and has the highest statistical power to predict SVR as well as relapse rates in HCV type 1-infected patients (Berg et al., 2006; Zeuzem et al., 2009; Puoti et al,. 2011), our findings showed that as the baseline HCV RNA value elevated, the probability of reaching SVR in patients with HCV-4 declined. In our series of patients, SVR was seen in 77.5% of HCV-4 patients with HCV RNA levels ($\leq 6 \times 10^5$ IU/ml) vs. 72.7% of those with HCV RNA levels ($> 6 \times 10^5$IU/ml), while 78.3% for ($\leq 8 \times 10^5$ IU/ml) vs. 68.4% for ($> 8 \times 10^5$ IU/ml), although this trend was not statistically significant. Similarly, Peignoux et al (2009) revealed that no significant difference between genotype 1 treatment naïve patients with baseline viral load $\leq 6 \times 10^5$ IU/ml and those $> 6 \times 10^5$ IU/ml (57% vs. 46% respectively).

As for gender as a host predictor of SVR, the current study supports Narciso-Schiavon et al (2010) in disclosing that there is no significant difference between males and females in attaining SVR. Other investigators showed that the response to combined therapy was poorer among female than among male hepatitis C-infected patients aged 50 years or older, irrespective of compliance (Berg et al., 2006; Kogure et al., 2008; Sezaki et al., 2009). On the contrary, women younger than 40 years of age had higher rates of SVR than did men (75% vs. 33%) (Hayashi et al., 1998)

Fibrosis is considered as one of the most important host predictors of SVR. In the present study patients with Metavir fibrosis score F_1 or F_2 had a significantly more frequent SVR compared with those with more advanced fibrosis F_3 (80.5% vs. 33.3%, p=0.006). These findings add support to many previous studies (Al-Faleh et al., 2000, 2004; Kamal et al., 2005, 2007; Gad et al., 2008; El Makhzangy et al., 2009; Bruno et al., 2010; Eskander et al., 2011) but contradict the findings reported by Khalil et al (2012) and Khairy et al (2013) who found that the grade of liver activity and fibrosis showed no statistically significant difference in achieving virological response.

In conclusion, RVR and pretreatment low fibrosis stages were the only statistically significant predicting factors for achieving SVR in genotype 4 naïve Egyptian hepatitis C virus-infected patients treated with the combination of pegylated interferon

and ribavirin for 48 weeks. On the contrary, age, pretreatment viral load and gender showed no statistical significant difference in achieving SVR. Physicians may then use the available data on predictors of response to interferon-based therapy in order to tailor the duration of the therapy of individual patients.

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