Effect of Prolongation of Combined Treatment in HCV-4 Infection

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Abstract: Background and aim: The recommended treatment for patients infected with hepatitis C virus (HCV) genotypes 1 and 4 is pegylated interferon plus ribavirin 1000 or 1200 mg/day for 48 weeks **[1].** Efforts to optimize and improve therapeutic outcomes are ongoing. Rapid virologic response (RVR) after 4 weeks of treatment and early virologic response (EVR) after 12 weeks of treatment play an important role in customization of therapy. In RVR patients who received 24 weeks of combined treatment but did not achieve SVR, the effect of prolongation of combined treatment on sustained virological response rate was not evaluated.**The current study** was to determine the effect of prolongation of combined treatment with pegylated interferon alfa-2a plus ribavirin to 48 weeks on increasing sustained virological response rate in patients infected with hepatitis C virus (genotype 4) who achieve rapid virological response. **Study design and methods** This study was conducted on 300 patients with chronic HCV genotype 4 infections who received combined treatment with peginterferon alfa-2a plus ribavirin. All patients were treatment naïve and older than 18 years with mean age of 42.15±9.5.Those patients who achieved RVR were randomly selected for 24 or 48 weeks of therapy. All patients received a combination of pegylated interferon α 2a 180ucg SC injection weekly plus ribavirin 800 – 1200 mg/day (dose adjusted according to body weight). All patients were adherent to treatment (all were compliant and did not develop any adverse effect that mandates either stoppage of treatment or reduction of the dose of either or both drugs),adherence to Treatment is defined as taking 80 % of each drug for at least 80 % of the duration of therapy **[6].**All patients were subjected to History taking, thorough clinical examination including funds examination, laboratory investigations including: fasting and post prandial blood glucose level, liver function tests, Alpha fetoprotein ,prothrombin time and INR, renal function tests, complete blood count, free T3,free T4, TSH, ANA, HIV and hepatitis C virus antibody using ELISA technique, HBsAg , HBs Ab, HBc Ab, HBeAg and HBe Ab.HCV RNA (PCR) in serum, both quantitative and qualitative and also HCV genotyping using INNO-LIPA HCVII test ,Qualitative HCV RNA PCR was done for all patients at week 4 of combined treatment to assess RVR.**For** those who achieved RVR**,** Qualitative HCV RNA PCR was done at week 24 for group A patients' and week 48 for group B patients' to assess end of treatment response (ETR).For those who achieved ETR**,** Qualitative HCV RNA PCR was done 24 weeks after stoppage of treatment to assess SVR,Abdominal ultrasonography, Liver biopsy was done for 17 patients only (as the rest of the participants denied such an invasive procedure).The biopsy specimen was fixed in 10% formalin then transferred to the pathology department. METAVIR scoring system was used to assess the histological lesions, Fibroscan was done for the rest of the patients. The operator who performed the liver stiffness measurement was unaware of neither the clinical nor the laboratory data of the patients. Results were expressed in kilopascals (kPa). The values used to correlate elastometry with METAVIR scoring system were as follows: 0-2.9 kPa for F0, 3-5.9 for F1, 6-8.9 for F2, 9-16.9 for F3 and 17-75 for F4**[8]** .This study was approved by the local ethical committee of Ain Shams University Hospitals and a written consent was obtained from each individual before participation in the study. **Results:** 57 patients who achieved RVR(19%) (Out of 300 patients who received treatment for chronic hepatitis C genotype 4) were included. All patients were treatment naïve and older than 18 years with mean age of 42.15±9.5. They were randomly assigned into two groups**. Group A:** 29 patients (22 males and 7 females) received combined treatment for 24 weeks with mean age 42.2.±9.2**Group B:** 28 patients (24 males and 4 females) received combined treatment for 48 weeks with mean age 42.1.±9.8.The differences between the two studied groups as regards the demographic data were insignificant; also there were insignificant differences between the two studied groups as regards pretreatment level of HCV viraemia, stages of fibrosis .The current study revealed an insignificant difference between the two studied groups as regards SVR and also statistically insignificant differences in SVR rates between rapid responders with different levels of viraemia whether treated for 24 or 48 weeks**.** There was a statistically insignificant difference in SVR rate between patients with F1 or F2 stages of fibrosis whether treated for 24 or 48 weeks, the same finding was observed among patients with F3 - F4 stages of fibrosis , however, the correlation between fibrosis stage and SVR was significant in both studied groups. **Conclusion;** Prolongation of standard combined treatment to 48 weeks does not influence SVR in HCV genotype 4 patients who achieve RVR while shortening of standard combined treatment to 24 weeks seems to be possible to all rapid responders without compromising their chance for achieving SVR.

[Yehia El Shazly, Salwa El Hadad, Wafaa Kamal, Mohamed Abdel Moghny, Reham Al Swaff, and Mohamed Hassan Fouad. **Effect of Prolongation of Combined Treatment in HCV-4 Infection.** *J Am Sci* 2013;9(3):284-292]. (ISSN: 1545-1003). http://www.jofamericanscience.org. 39

Keywords: prolonged combined treatment, HCV-4 infection.

1. Introduction

The recommended treatment for patients infected with hepatitis C virus (HCV) genotypes 1 and 4 is pegylated interferon plus ribavirin 1000 or 1200 mg/day for 48 weeks **[1].**

Efforts to optimize and improve therapeutic outcomes are ongoing. Rapid virologic response (RVR) after 4 weeks of treatment and early virologic response (EVR) after 12 weeks of treatment play an important role in customization of therapy,They have been shown to be strong predictors of response **[2].**

Patients with HCV genotype 1 infection who achieve RVR have a high chance of achieving SVR after just 24 weeks of treatment with peginterferon alfa-2a plus ribavirin 1000-1200 mg/day **[3].** On the contrary, Patients with HCV genotype 1 infection who fail to achieve RVR may be considered difficult to cure and some of them might benefit from an extended period of treatment **[4].**

Patients with HCV genotype 1 or 4 infection who achieved RVR with peginterferon alfa-2a plus ribavirin 1000-1200 mg/day are successfully treated with SVR rate of 87 percent **[5].**

In RVR patients who received 24 weeks of combined treatment but did not achieve SVR, the effect of prolongation of combined treatment on sustained virological response rate was not evaluated. **The aim of the current study** was to determine the effect of prolongation of combined treatment with pegylated interferon alfa-2a plus ribavirin to 48 weeks on increasing sustained virological response rate in patients infected with hepatitis C virus (genotype 4) who achieve rapid virological response.

2. Patients and Methods:

The current study was conducted in the Gastroenterology and Hepatology unit, department of internal medicine, AIN SHAMS university hospitals, Cairo, Egypt, in the period between May 2009 and April 2012. The study was a double blind randomized controlled study including 300 patients with chronic HCV genotype 4 infection who received combined treatment with peginterferon alfa-2a plus ribavirin. All patients were treatment naïve and older than 18 years with mean age of 42.15±9.5.

Those patients who achieved RVR were randomly selected for 24 or 48 weeks of therapy. All patients received a combination of pegylated interferon α 2a 180ucg SC injection weekly plus ribavirin 800 – 1200 mg/day (dose adjusted according to body weight). All patients were adherent to treatment (all were compliant and did not develop any adverse effect that mandates either stoppage of treatment or reduction of the dose of either or both drugs),adherence to Treatment is defined as taking 80 % of each drug for at least 80 % of the duration of therapy [6].

All patients were subjected to the following

- History taking, thorough clinical examination including funds examination, laboratory investigations including: fasting and post prandial blood glucose level, liver function tests, Alpha fetoprotein ,prothrombin time and INR, renal function tests, complete blood count, free T3,free T4, TSH, ANA, HIVand hepatitis C virus antibody using ELISA technique, HBsAg, HBsAb, HBcAb, HBeAg and HBeAb.
- HCV RNA (PCR) in serum, both quantitative and qualitative by Real time PCR (using comas ammplicor HCV 2.0. Roche molecular system) Qualitative HCV RNA PCR was done for all patients at week 4 of combined treatment to assess RVR.

For those who achieved RVR:

Qualitative HCV RNA PCR was done at week 24 for group A patients' and week 48 for group B patients' to assess end of treatment response (ETR).

For those who achieved ETR:

Qualitative HCV RNA PCR was done 24 weeks after stoppage of treatment to assess SVR

- HCV genotyping using INNO-LIPA HCVII test. This test is based on reverse hybridization of 5' untranslated region PCR amplification product.
- Abdominal ultrasonography (Aloka SSD620, Japan) using 3.5 MHZ convex probe.
- Liver biopsy was done for 17 patients only (as the rest of the participants denied such an invasive procedure).

After a written consent and a bleeding profile (Prothrombin time, partial thromboplastin time and platelet count), Ultrasound-guided percutaneous liver biopsy was done. After adequate skin sterilization and local anesthesia, liver biopsy was done through intercostals approach guided by abdominal ultrasound with the patient holding his breath at the end of a quit expiration, using automated tru-cut needle, G18, 16cm length (sample length of 1.7cm) supplied by Gallini medical product, Mirandola, Italy.During the first hour after the procedure, pulse and blood pressure were measured every 15 minutes then every 30 minutes for the next two hours. The

patient remained recumbent in the right lateral position for 6 hours.The biopsy specimens was fixed in 10% formalin then transferred to the pathology department.METAVIR scoring system was used to assess the histological lesions.

- Fibroscan was done for the rest of the patients. Fibroscan is designed for noninvasive assessment of liver fibrosis and is based on elastometry (or one dimensional transient elastography), harder the tissue, faster the shear wave propagates ***[7].*** The tip of the transducer probe was placed on the skin, between the ribs, at the level of the right lobe. Once the target area has been located, acquisition was triggered by pressing a button. The measurement depth is between 25 and 65 mm below the skin surface. In this study, at least five successful measurements were made in each patient. The median value of all successful acquisitions in each patient was recorded as the liver elastic modulus. The operator who performed the liver stiffness measurement was unaware of neither the clinical nor the laboratory data of the patients. Results were expressed in kilopascals (kPa). The values used to correlate elatometry with METAVIR scoring system were as follows: 0-2.9 kPa for F0, 3-5.9 for F1, 6-8.9 for F2, 9-16.9 for F3 and 17-75 for F4**[8].**
- **METAVIR** scoring system is one of the few validated scoring systems. This system assesses histological lesions in chronic hepatitis C using two separate scores, one for necroinflammatory grade and another for the stage of fibrosis. These scores are defined as follows:

Stages of fibrosis (F): F0: no fibrosis; F1: portal fibrosis without septa; F2: portal fibrosis with rare septa, F3: numerous septa without cirrhosis; F4: cirrhosis.

Grade for activity (A): A0: no necroinflammatory activity; A1: minimal activity, A2: moderate activity, A3: severe activity.

The intra- and inter-observer variations of this METAVIR scoring system are lower than those of the widely used Knodell scoring system. For METAVIR fibrosis stages there is an almost perfect concordance ***[8].***

- This study was approved by the local ethical committee of Ain Shams University Hospitals and a written consent was obtained from each individual before participation in the study.

Exclusion Criteria:

- Patients with decompensated cirrhosis.
- Patients with hepatocellular carcinoma.
- Current pregnancy or breastfeeding.
- Prior or current anti viral therapies.
- Regular or excessive alcohol consumption.
- Other liver diseases as alcoholic liver disease, non alcoholic fatty liver disease (NAFLD), drug-induced hepatitis, other viral hepatitis, hereditary haemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis and α1 antitrypsin deficiency.
- Obese patients (BMI $\geq$30).
- Current intravenous drug abuse.
- Neutropenia (< 1500/mm3).
- Thrombocytopenia (<90000/mm3).
- Serum Creatinine more than 1.5 times the upper limit of normal value.
- Severe cardiac, pulmonary, retinal, thyroid, or psychiatric disorders.
- HIV infection.
- Patients who received any form of antiviral therapy.
- Patients who refused to participate in the study.

Statistical methods:

The data was collected, coded and entered to a personal computer, IBM compatible 3 GHz. The data was analyzed with the program Statistical Package for Social Science (SPSS) 16 for Windows operating system. The following tests were used: calculation of the mean value, Student's t-test, Pearson correlation test and Chi-square test (χ^2). The probability of error (P) was expressed as following: P-value > 0.05: non-significant (NS), P-value ≤ 0.05: significant (S), P-Value <0.01: highly significant (HS).

3. Results:

The current study showed that 57 patients who achieved RVR (out of 300 patients who received treatment for chronic hepatitis C genotype 4) were included. RVR rate among studied patients was 19%. All patients were treatment naïve and older than 18 years with mean age of 42.15±9.5.

29 patients (22 males and 7 females) were randomly assigned to group A and received combined treatment for 24 weeks. The mean age of group A patients' was 42.2.±9.2

28 patients (24 males and 4 females) were randomly assigned to group B and received combined treatment for 48 weeks. . The mean age of group B patients was 42.1.±9.8

The current study revealed an insignificant difference between the two studied groups as regards SVR; also there were statistically insignificant differences in SVR rates between rapid responders with different levels of viraemia whether treated for 24 or 48 weeks **(tables 1, 2).** The differences between the two studied groups as regards the demographic data were insignificant; also there were insignificant differences between the two studied

groups as regards pretreatment level of HCV viraemia, stages of fibrosis **(tables 3, 4).**

There was a statistically insignificant difference in SVR rate between patients with F1 or F2 stages of fibrosis whether treated for 24 or 48 weeks, the same finding was observed among patients with F3 - F4 stages of fibrosis **(table 5).**

There were insignificant correlations between SVR in one hand and gender, age, BMI, pretreatment ALT level, pretreatment level of viraemia on the other hand **(tables 6-13)** , however the correlation between fibrosis stage and SVR was significant in both studied groups **(tables 9,13).**

Table 1: Comparison between the two studied groups as regard SVR

SVR	Responders No. %	Non resp. No. %	X2	P
Group A SVR (48 W) N=29	22 75.9	7 24.1	0.8	0.3
Group B SVR (72W) N=28	24 85.7	4 14.3		

Table 2: Comparison between the two studied groups as regard pretreatment viral load and SVR

SVR / Viral Load	Responders No. %	Non responders No. %	X2	P
(>600000 IU/ml) Group A(N=10)	4 40.0	6 60.0		
(>600000 IU/ml) Group B(N=12)	9 75.0	3 25.0	1.5	0.2
(<600000IU/ml) Group A (N=19)	18 94.73	1 5.27	0.34	0.54
(<600000IU/ml) Group B (N=16)	15 93.75	1 6.25		

Table 3: Comparison between the two studied groups as regard pretreatment level of HCV viraemia.

	Group A Mean SD	Group B Mean SD	t	P
HCV RNA	960.4 1337.0	1019.9 1265.3	0.1	0.8

Table 4: Comparison between the two studied groups as regard stages of fibrosis.

	<F3 No. %	≥F3 No. %	X2	P
Group A	23 79.3	6 20.7		
Group B	19 67.9	9 32.1	0.9	0.3

Table 5: Comparison between SVR in group A and Group B regarding patients with F1-F2, F3-F4 stages of fibrosis

	Responders No. %	Non responders No. %	X2	P
F1-F2 Group A(N=23)	21 91.3	2 8.7	0.3	0.56
F1-F2 Group B(N=19)	19 100	0 0		
F3-F4 Group A (N=6)	1 20	5 80	0.9	0.33
F3-F4 Group B (N=9)	5 55.6	4 44.4		

Table 6: Correlation between gender, BMI and SVR in Group A

	Responders No. %	Non resp. No. %	X2	P
Males (N=22)	17 77.3	5 22.7		
Females (N=7)	5 71.4	2 28.6	0.09	0.7
Average weight (N=9	8 88.9	1 11.1		
Overweight(N=20)	14 70.0	6 30.0	1.2	0.2

Table 7: Correlation between age and SVR in Group A

Age	Mean	SD	t	P
Responders (N=22)	41.6	8.2		
Non responders (N=7)	43.8	12.4	0.5	0.5

Table 8: Correlation between pretreatment ALT level and SVR in Group A

ALT	Mean	SD	t	P
Responders N=22	73.0	46.3		
Non responders N=7	57.1	33.6	0.8	0.4

Table 9: Correlation between stages of fibrosis and SVR in Group A

	Responders No. %	Non resp. No. %	X2	P
F1(N=4)	4 100.0	0	19.2	0.00
F2(N=19)	17 89.5	2 10.5		
F3(N=5)	0	5 100.0		
F4(N=1)	1 100.0	0		

Table 10: Correlation between gender, BMI and SVR in Group B

	Responders No. %	Non resp. No. %	X2	P
Males (N=24)	21 87.5	3 12.5	0.4	0.5
Females (N=4)	3 75.0	1 25.0		
Average weight (N=5)	5 100.0	0	1.0	0.3
Over weight (N=23)	19 82.6	4 17.4		

Table 11: Correlation between age, and SVR in Group B

Age	Mean	SD	t	P
Responders (N=24)	40.8	9.7	1.8	0.07
Non responders (N=4)	50.2	6.2		

Table 12: Correlation between pretreatment ALT level and SVR in Group B

ALT	Mean	SD	t	P
Responders (N=24)	64.0	47.2	0.1	0.9
Non responders (N=4)	61.2	65.0		

Table 13: Correlation between stage of fibrosis and SVR in Group B

	Responders No. %	Non resp. No. %	X2	P
FS 1(N=4)	4 100.0	0	7.3	0.007
FS 2(N=15)	15 100.0	0		
FS 3(N=7)	4 57.1	3 42.9		
FS 4(N=2)	1 50.0	1 50.0		

4. Discussion:

The current standard of care for treatment of chronic HCV-4 infection is a combination of pegylated interferon alpha and ribavirin for 48 weeks. Treatment response in patients who have chronic HCV infection is quite heterogeneous and depends on host factors (i.e., age, gender, alanine aminotransferase levels, stage of fibrosis, insulin resistance) and viral factors, such as serum concentration of HCV RNA at the time of initiation of antiviral therapy and HCV genotypes **[9].**

It is suggested that treatment can be generally shortened in rapid responders especially those with low viral load and prolonged in early responders. Several studies have shown that 24 weeks of therapy is sufficient to induce SVR in chronic HCV-4 patients achieving RVR. Clinical data suggest that in patients with chronic HCV-4 and undetectable HCV RNA at weeks 4 and 12, treatment with PEG-IFN-2 and ribavirin for 24 weeks and 36 weeks, respectively, is sufficient **[10].**

To the best of our knowledge, the current study was the first to assess the effect of prolongation of combined treatment to 48 weeks on SVR rate in hepatitis C virus genotype 4 infected patients who achieve RVR.

The current study was a randomized controlled study that included 300 patients with chronic HCV-4 infection who received combined treatment with peginterferon alfa-2a plus ribavirin. The 57 patients who achieved RVR (19%) were randomly selected for 24 or 48 weeks of therapy.

SVR rates were comparable in the 24 and 48 treatment weeks (TW) arms suggesting the absence of compromise in SVR when treating rapid virological responders for 24 weeks duration.

The results of the current study agree with the results of the study performed by **Poordad et al (2010)** where 5270 HCV-1 patients received PEG-IFN alfa plus ribavirin and were evaluated for RVR. Of those, 891 (16.9%) had undetectable HCV RNA at week 4 of therapy; 288 were treated for 24 weeks, and 603 were treated for 48 weeks. Of the 288 patients treated for 24 weeks, 224 attained SVR (77.8%). Similarly, of the 603 patients who attained RVR and were treated for 48 weeks, 517 attained SVR (85.7%). The difference between both groups as regards SVR was insignificant. Overall, these observations tend to support the use of a 24-week regimen among G1 patients who attain RVR **[11].**

As HCV-4 and HCV-1 are both considered difficult to treat, it seems logic to compare between both groups especially regarding SVR and duration of treatment.

In support to this conclusion, **Ferenci and Laferl (2008)** reported the rate of sustained virological response in patients infected with hepatitis C virus genotype 1 or 4 who were assigned to 24 weeks of treatment with pegylated interferon alfa-2a 180 mug/wk plus ribavirin 1000/1200 mg/day after achieving a rapid virological response in a prospective trial investigating response-guided therapy. A total of 150 of 516 patients (29%) had an RVR, 143 of which completed 24 weeks of treatment. Younger patients, leaner patients, and those with an HCV RNA level $\leq$ or = 400,000 IU/mL and HCV genotype 4 infection were more likely to achieve an RVR. The SVR rate was 80.4% (115/143) in patients who completed 24 weeks of treatment. The SVR rate was 86.7% (26/30) in patients infected with genotype 4 and 78.8% in those infected with genotype 1 (89/113). This study confirms that a 24-week regimen of peginterferon alfa-2a plus ribavirin 1000/1200 mg/day is appropriate in genotype 1 and 4

patients with a low baseline HCV RNA level who achieve an RVR **[12].**

The results of the current study are also consistent with the results of the study performed by **Mangia et al (2008).** In that study, 696 patients were included, 237 of which received standard combined therapy for 48 weeks regardless their viral kinetics, while 459 of which received standard combined therapy for 24, 48, or 72 weeks depending on HCV-RNA negativity at weeks 4, 8, or 12, respectively. SVR in rapid responders who received 24 weeks of standard combined treatment was 77.2% compared to 87% in rapid responders who received 48 weeks of standard combined treatment. The difference was insignificant between the two groups favoring 24 weeks of treatment in HCV patients with RVR **[13].**

In contrast to the current study came the results of **Yu et al (2008)** who assessed whether treatment duration of 24 weeks is as effective as standard treatment in HCV-1 patients with a rapid virological response. Two hundred HCV-1 Asian patients were randomized (1:1) to either 24 or 48 weeks of peginterferon-alpha-2a (180 ug/week) and ribavirin (1000-1200 mg/day). 87 patients (43.5%) achieved RVR. Those in the 24-week arm had a lower SVR rate (88.9%) than the 48-week arm (100%). The study concluded that HCV-1 patients derive a significantly better SVR from 48 weeks versus 24 weeks of peginterferon/ribavirin even if they attain an RVR **[14].**

However, this contradiction may be related to racial differences between Egyptian and Asian patients, viral genotype 1 and 4 specific differences and/or unequal number of patients included in each study.

Based on the result of the present study, the duration of combined treatment with pegylated interferon and RBV should not be prolonged to 48 weeks of therapy in every HCV -4 infected patient who achieve RVR, but may rather be specifically individualized according to other viral and patients' pretreatment characteristics.

Accordingly, other factors which may influence response to combined treatment in HCV -4 infected patients who achieve RVR were evaluated by the current study and revealed the following:

Regarding the influence of pretreatment viral load on SVR rate, the current study revealed insignificant differences in SVR rates between rapid responders with low (< 600000 IU/ml) and high (> 600000 IU/ml) viral loads in the 24 versus 48 TW arms. However, it is worth to admit that the sample size of patients with low and high viral loads was small which reduced the power to detect any significant difference between the studied groups.

These results partially agree with the results of the study performed by **Liu et al (2008).** In that multicenter, randomized trial, 308 treatment-naive HCV-1 infected Asian patients were randomly assigned to receive either 24 or 48 weeks of pegylated IFN-alpha-2a plus ribavirin. Among patients with a baseline serum HCV RNA level <800,000 IU/mL and RVR, SVR rates were comparable between 24- and 48-week courses of therapy (94% vs. 100%; P= 0.13). The study concluded that Patients with a baseline serum HCV RNA level <800,000 IU/mL who achieve an RVR can receive a 24-week of therapy without compromising the SVR rates; however, other patients with non-matching criteria should receive a 48 week course of therapy **[15].**

These results also partially agree with the previously mentioned study by **Yu et al (2008)** who concluded that among chronic HCV-1 rapid responders with low pretreatment viral load, SVR rates were comparable in those patients receiving 24 and 48 TW (96% versus 100%), however in patients with high pretreatment viral load, 48 TW arm had significantly higher SVR rates than 24 TW arm (100% versus 76.5% respectively) **[14].**

This conclusion also agree with **Zeuzem etal (2006) [16]** who studied 235 HCV-1 infected patients with low pretreatment viral load (<600000 IU/ml) who received combined therapy for 24 weeks and were compared with a historical 48 week control group in **Manns et al (2001)**. In the subgroup of rapid virologic responders, SVR rates were comparable in the 24 and 48 TW arms being 89% and 85% respectively. The study concluded that among chronic HCV-1 rapid responders with low pretreatment viral load, SVR rates were comparable in those patients receiving 24 and 48 TW**[25].**

The results of the current study and supporting previous literature highlight the fact that shortening of standard combined treatment to 24 weeks in HCV-4 infected patients with low pretreatment viral load who achieve RVR does not compromise their chance to achieve SVR. Further studies should be conducted on larger scale of HCV-4 patients with moderate and high pretreatment viral load to properly evaluate the effect of prolongation of combined treatment on SVR rate in such patients.

Regarding the impact of the stage of liver fibrosis on SVR rate, the current study revealed significantly higher SVR rates among patients with F1-F2 stages of fibrosis as compared to patients with F3-F4 stages of fibrosis (in both studied groups).In addition, There was insignificant difference in achieving SVR in F1-F2 patients who received either 24 or 48 TW, similar results was found among patients with F3-F4 stages of fibrosis.

These results agree with **Yu etal (2008)** in which SVR rates were 81.4% and 78.5% in F1-F2 patients receiving 24 and 48 TW respectively, while SVR rates were 18.6% and 21.5% in F3-F4 patients receiving 24 and 48 TW respectively. **[14].**

In discordance with the current results, **Khattab et al (2011)** proposed an algorithm for treating patients with chronic HCV-4 based on the kinetics of viral response (response-guided therapy) where rapid responders with predictors of poor response (Viral load > 800000, F3 or F4 and HOMA-IR≥2) had to be treated for 48 TW, while those with no predictors of poor response had to be treated only for 24 weeks **[17].**

Based on the current results and supporting previous literature, it is concluded that the stage of fibrosis is a highly significant predictor of SVR in RVR patients receiving either 24 or 48 TW of combined treatment.

Patient's age is a well known factor that is associated with responsiveness to Pegylated interferon α/ribavirin therapy in chronic HCV infection. Generally, it is believed that younger individuals (usually < 40 years of age) respond better to IFN-α treatment than older persons **[18].**The obvious explanation is that older HCV patients are likely to have more advanced liver disease, such as fibrosis and cirrhosis (themselves predictors of poor virological responses) **[19].**

Strikingly, the present study revealed an insignificant correlation between age and SVR in RVR patients receiving either 24 or 48 TW of combined treatment.

This result agrees with Yu et al., 2008 who concluded that among chronic HCV-1 rapid responders who received 24 or 48 TW, mean age had an insignificant impact on SVR **[14].**

This result also agrees with **Floreani et al** (2011) who studied 74 patients with HCV-1 & HCV-4 who were treated for 48 weeks with standard combined therapy. 74.3% of those patients achieved SVR. The mean age of the study group was 42.9±10.7. Floreani compared patients ≤50 year old to patients >50 year regarding SVR. There was insignificant difference between the two groups suggesting that age is a non-significant predictor of SVR in such patients. **[20].**

Also in accordance with these results, **Pineda et al** (2010) studied 154 patients of HCV-1, 3, 4 treated with standard combined therapy for 48 weeks, of which 50% achieved SVR. 52% of patients ≤42 year old achieved SVR, whereas 47% of patients >42 year old achieved SVR. An insignificant difference was found between the two groups as regards SVR **[21]**.In discordance with these results, **Jeffers etal (2004)** studied 108 HCV-1 patients who received combined therapy for 48 weeks. They compared patients ≤40 and >40 years of age regarding SVR and found a significant correlation between age and SVR **[22].**However, Jeffers et al studied a specific population of Black Americans who were treated for 48 treatment weeks, they were not necessarily rapid responders at time of randomization into study groups.

The current study also evaluated the effect of gender on achieving SVR to combined treatment with pegylated interferon α2a and ribavirin in chronic HCV genotype 4 infection. Insignificant higher SVR rates were found among male patients as compared to females in both studied groups.

These results agree with **Yu et al (2008)** who concluded that among chronic HCV-1 rapid responders who received 24 or 48 TW, gender had an insignificant impact on SVR **[14].**

These results also agree with **Antonov et al (2011)** who studied 71 HCV-1 patients who received combined treatment for 48 weeks. The correlation between gender and SVR was insignificant **[23].**

Pineda et al (2010) studied 154 patients with HCV-1,3, 4 who received combined treatment for 48 weeks. 50% of the patients achieved SVR. 46% of male patients achieved SVR, whereas 71% of female patients achieved SVR. In contrast to the current study, there was a significant difference between male and female patients regarding SVR **[21].**However, this contradiction could be explained by the fact that Pineda studied mixed genotypes who received standard combined treatment for 48 weeks. Also, initial patient selection criteria did not necessitate RVR.

Regarding the effect of BMI on SVR, an insignificant higher SVR rate was found among average weight patients as compared to overweight patients receiving either 24 or 48 TW of combined treatment.

These results agree with **Yu etal (2008)** who concluded that among chronic HCV-1 rapid responders who received 24 or 48 TW, pretreatment BMI had an insignificant impact on SVR **[14].**

These results also agree with **Floreani etal (2011)** who studied 74 patients with HCV-1, 4. 74.3% of those patients achieved SVR. The mean BMI of those patients was 23±3. The correlation between BMI and SVR was insignificant **[20]**

The results of the present study also agree with **Pineda etal (2010)** who studied 154 patients with HCV-1, 3, 4. 50% of those patients achieved SVR. 52% of patients with BMI<23 achieved SVR whereas 48% of patients with BMI≥23 achieved SVR. The difference between both groups as regards SVR was insignificant **[21].**

These results highlight the low value of BMI as a patient specific pre-treatment predictor for assessing the likelihood of achieving SVR in HCV-4 infected patients who achieve RVR whether treated for either 24 or 48 weeks.

Serum ALT level is recognized as a marker reflecting the degree of the histological damage and has served as a parameter for starting therapy or judging response to antiviral treatment in chronic hepatitis C **[24].**

The current study revealed higher SVR rates was among cases with higher mean pretreatment ALT level as compared to cases with lower mean ALT level in both studied groups but those differences were statistically insignificant.

The current results agree with **Yu etal , 2008** who concluded that among chronic HCV-1 rapid responders who received 24 or 48 TW, pretreatment ALT had an insignificant impact on SVR **[14].**

The current results also agree with **Antonov et al (2011)**who studied 71 HCV-1 patients who received standard combined treatment for 48 weeks. ALT was insignificant in prediction of SVR. However in that study, all patients were HCV-1 and they were treated for 48 weeks regardless their status of rapid virologic response **[23].**

In discordance with these results, **Torres et al (2009)** performed a study on 269 latino and 300 non latino HCV-1 patients who received combined therapy for 48 weeks. Baseline ALT was significant in predicting SVR in non latino patients. However, patients were randomized according to race rather than rapid virologic response and they all completed 48 treatment weeks **[25].**

Conclusion;

Prolongation of standard combined treatment to 48 weeks does not influence SVR in HCV genotype 4 patients who achieve RVR, while shortening of standard combined treatment to 24 weeks seems to be possible to all rapid responders without compromising their chance for achieving SVR.

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1/28/2013