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Rapid virological response tailors the duration of treatment in hepatitis C virus genotype 3 patients treated with pegylated interferon alfa-2a and ribavirin in Pakistan

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SUMMARY

Background: Rapid virological response (RVR) is now thought to be the strongest predictor of sustained virological response (SVR) in hepatitis C virus (HCV) patients undergoing antiviral therapy. It can be used as a guide to individualize treatment duration. The aim of this study was to assess the role of RVR in tailoring the duration of treatment.

Methods: Patients with HCV genotype 3 infections were enrolled and treated with pegylated interferon alfa-2a (PEG IFN alfa-2a) 180 μg/week and ribavirin. HCV RNA was analyzed at weeks 4, 12, 16, and 24. Treatment duration was individualized on the basis of RVR. Patients who achieved RVR and who were aged ≤40 years with a body mass index (BMI) ≤27 kg/m^2 received 16 weeks of treatment (group A). Patients who achieved RVR and were aged >40 years with a BMI >27 kg/m^2, aged >40 years with a BMI ≤27 kg/m^2, and aged ≤40 years with a BMI >27 kg/m^2 received 24 weeks of treatment (group B). Patients who did not achieve RVR but who achieved an early virological response (EVR; HCV PCR-negative or ≥2 log drop in HCV RNA at week 12) were treated with 24 weeks of therapy (group C).

Results: SVR was observed in 86% in group A, 82.2% in group B, and 46.8% in group C. A difference was observed in SVR for patients with and without RVR and receiving the standard duration of treatment (82.2% vs. 46.8%, $p < 0.001$). The results show that the rate of SVR is not inferior in those with RVR treated with 16 weeks of therapy compared to 24 weeks (86% vs. 82.2%, $p = 0.004$).

Conclusions: RVR is useful to individualize the duration of treatment and to predict the treatment outcome. A short treatment of 16 weeks is as effective as 24 weeks in HCV genotype 3 patients who achieve RVR, who have a low BMI, and are younger in age.

1. Introduction

Hepatitis C virus (HCV) constitutes a major public health issue in Pakistan, with 4.8% of people living with this virus.[1] In developing countries, the major problem is the poor socio-economic situation of the patients.[2] Pegylated interferon (PEG IFN) and ribavirin are expensive and people have difficulty in affording this therapy. Therefore early detection of virological failure helps to reduce additional costs and the adverse effects of infective therapy. Moreover, a rapid virological response (RVR; PCR-negative at week 4 of therapy) best predicts a sustained virological response (SVR). It can be used as a guide to individualize the duration of treatment. An individualized treatment approach improves cost-effectiveness of HCV antiviral therapy by decreasing side effects and the cost of therapy.[3]

HCV genotype is an important predictor of treatment response, therefore the duration of treatment for HCV is based on HCV genotype: 24 weeks is recommended for genotypes 2 and 3, and 48 weeks for genotypes 1 and 4.[4,5] Preliminary clinical data have shown that a shorter course of therapy is as effective as a 24-week treatment regimen for patients with HCV genotype 2 or 3, especially those with RVR.[6–9] However, it is important to determine whether these results are applicable to other populations.

The most prevalent HCV genotype in the Pakistani population is type 3, which has a favorable response to interferon.[10] The primary aim of this prospective cohort study was to evaluate whether a 16-week regimen of PEG IFN and ribavirin is sufficient to achieve SVR among patients who achieve RVR.

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2. Patients and methods

2.1. Patient selection

Treatment-naïve HCV genotype 3 patients aged >16 years, males and females, were enrolled in the study using the following criteria: anti-HCV antibody-positive and positive PCR for HCV RNA detection. Furthermore the patients had to be negative for hepatitis B surface antigen and not suffering from decompensated liver disease or autoimmune disorders; they also had to have no history of depression or cardiac diseases.

Prior to starting treatment, the patient's complete blood count, prothrombin time, alanine aminotransferase (ALT), quantitative HCV RNA, and genotype were determined. All patients in the study were required to have a hemoglobin level above 13 g/dL in men and 12 g/dL in women, a white blood cell count greater than 3×10^9/L, and a platelet count greater than 100×10^9/L. Normal levels of serum albumin and normal thyroid function tests were also required. Patients who were under 16 years or above 70 years of age and pregnant women were excluded from the study.

2.2. Study design

This study was conducted at Maroof International Hospital from May 2009 to June 2011. The protocol was approved by the ethics review committee of the hospital and informed written consent was obtained from all of the participants. The study was designed by the Digestive Disease Study Group of Maroof International Hospital. A total of 495 patients were screened. Among them 485 fulfilled the study criteria and were enrolled for antiviral therapy. Therapy was started with PEG IFN alfa-2a 180 μg weekly and ribavirin 400 mg twice daily. The treatment duration was individualized on the basis of qualitative HCV analysis at week 4 after the start of treatment. Patients who were HCV PCR-negative at week 4 were allocated to one of two groups (group A, group B). Patients who achieved RVR and who were aged ≤40 years with a BMI ≤27 kg/m^2 received 16 weeks of treatment (group A). Patients who achieved RVR and who were aged >40 years with BMI >27 kg/m^2, aged >40 years with BMI ≤27 kg/m^2, and aged ≤40 years with BMI ≥27 kg/m^2 received 24 weeks of treatment (group B). Patients who did not achieve RVR but who achieved an early virological response (EVR; HCV PCR-negative or ≥2 log drop in HCV RNA at week 12) were treated with 24 weeks of therapy (group C). Patients with a <2 log drop in viral load at week 12 were considered non-responders and the therapy was discontinued. All of the patients were followed up for 24 weeks after the end of therapy (Figure 1).

2.3. Measurement of HCV RNA and HCV genotype

Serum HCV RNA levels were evaluated quantitatively by real-time PCR (Rotor-Gene 3000, Corbet Research; 50 IU/ml) at baseline,

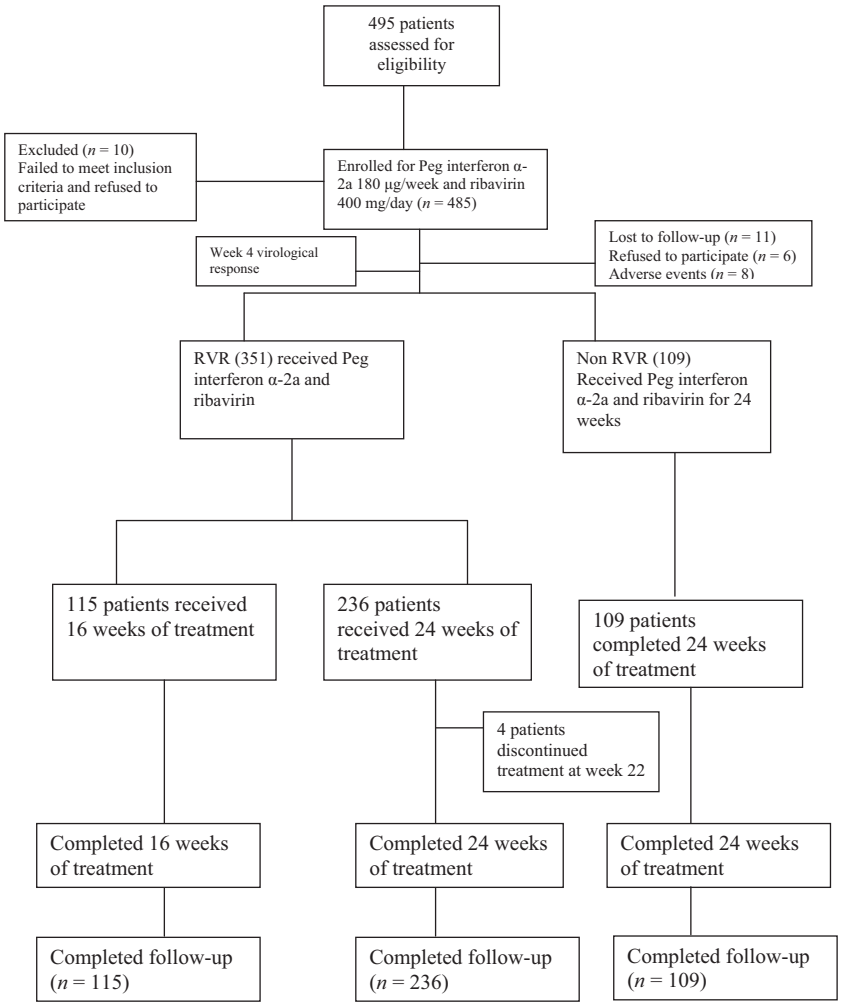

Figure 1. Flow diagram of patient enrollment, and disposition of patients treated with PEG IFN alfa-2a.

week 4, at the end of treatment, and at 24 weeks after the end of treatment. HCV genotyping was performed using the Invader HCV genotyping assay developed by Third Wave Technologies, Inc.[11]

2.4. Assessment of efficacy

The primary end-point of this study was to assess SVR, which is defined as undetectable HCV RNA at 6 months after the end of treatment; non-responders were those who had a <2 log drop in HCV RNA at week 12 of treatment. RVR is defined as undetectable HCV RNA at 4 weeks of treatment. Patient relapse was defined as reappearance of HCV RNA during the follow-up period in patients who had achieved negative HCV RNA at the end of treatment.

2.5. Statistical analysis

Data were analyzed using SPSS version 15 for windows (SPSS Inc., Chicago, IL, USA). The results for all variables are given in the form of the rate (%). The Pearson Chi-square method was used to measure variable associations with the likelihood of achieving SVR. A *p*-value below 0.05 was considered significant. Multivariate logistic regression analysis was performed to identify factors associated with a response to therapy. Variables with associations in the univariate analysis were entered into the multivariate logistic regression analysis to identify independent predictors of treatment outcome.

3. Results

Four hundred and ninety-five patients suffering from HCV genotype 3 infections were recruited from May 2009 to June 2011. Of these, 460 completed treatment; 210 (45.6%) were male and 250 (54.3%) were female. Adverse events resulting in patients dropping out at week 4 included rash, headache, fatigue, and emotional instability. Moreover one patient withdrew from treatment at week 22 due to anemia. Overall, RVR was achieved in 351 (76.3%) patients. The characteristics of the study patients are presented in Table 1.

Overall, SVR was achieved in 344 (74.8%) patients. The SVR rate observed in group A was 86% (99 patients), in group B was 82.2% (194 patients), and in group C was 46.8% (51 patients), as shown in Figures 2 and 3. SVR rates were compared between group B patients (those who achieved RVR and had 24 weeks of treatment) and group C patients (those who did not achieve RVR and received 24 weeks of treatment). These patients were re-assessed at week 12 and we did not find any patient who met the criteria for a non-responder. However, SVR rates were significantly higher in group B patients (24 weeks of treatment) who had RVR as compared to group C patients (24 weeks of treatment) who did not have RVR: 82.2% vs. 46.8%, $p < 0.001$. Moreover result shows that the rate of SVR is not inferior in those with RVR treated with 16 weeks of therapy compared to 24 weeks of therapy (86% vs 82.2%, $p = 0.004$).

Table 1
Basic characteristics of the 460 patients who completed treatment in this study

Characteristics	All patients	Patients with RVR	With No RVR
Sex			
Male	210	153 (72.8%)	57 (27.1%)
Female	250	198 (79.2%)	52 (20.8%)
Age, years			
≤40	236	195 (82.6%)	41 (17.3%)
>40	224	156 (69.6%)	68 (30.3%)
Viral load, IU/ml			
$\leq 8 \times 10^5$	185	150 (81.0%)	35 (18.9%)
$>8 \times 10^5$	275	201 (73.0%)	74 (26.9%)
ALT			
Normal	97	76 (78.3%)	21 (21.6%)
Raised	368	275 (74.7%)	88 (23.9%)
BMI, kg/m^2			
≤27	335	260 (77.6%)	75 (22.4%)
>27	125	91 (72.8%)	34 (27.2%)
Route of transmission			
Dentist	157	117 (74.52%)	40 (25.47%)
Blood transfusion	10	7 (7%)	3 (30%)
Unsterilized surgical instrument	72	47 (65.27%)	28 (38.8%)
Unknown source	76	60 (79%)	16 (21%)

RVR, rapid virological response; ALT, alanine aminotransferase; BMI, body mass index.

3.1. Predictors of a sustained virological response

Both pretreatment and treatment factors that could be associated with the response to the therapeutic regimen were compared between patients with and without SVR. The preliminary analysis showed that rates of SVR were higher in patients aged ≤40 years as compared to patients aged >40 years (82.6% vs. 66.5%, $p < 0.0001$). We did not find a significant difference for SVR

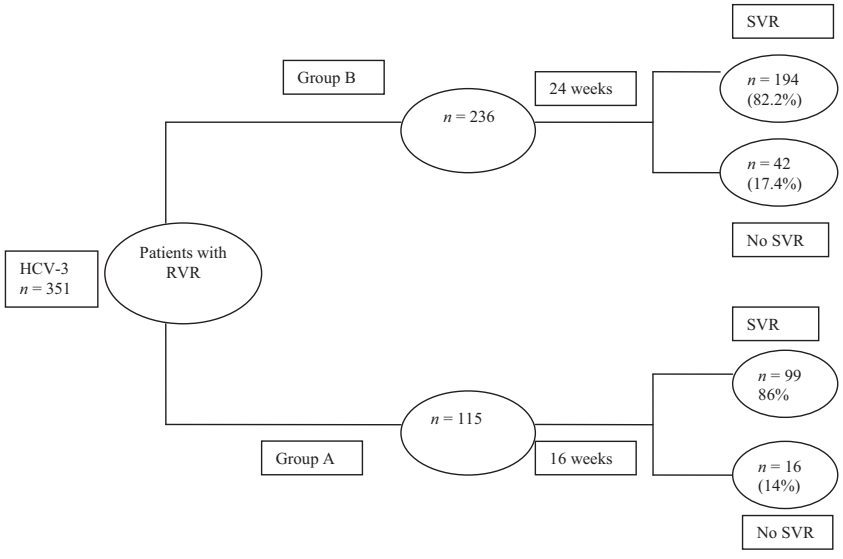

Figure 2. Predictability of SVR in the 16-week and 24-week treatment groups with RVR.

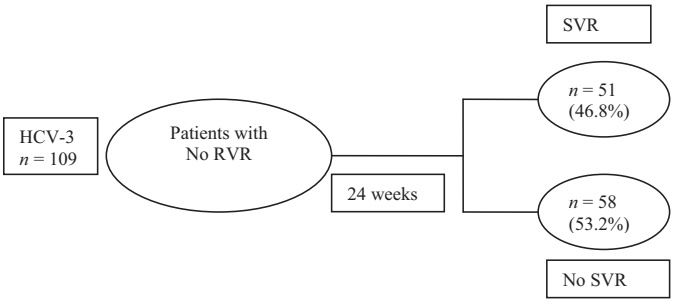

Figure 3. Predictability of SVR in the 24-week treatment group without RVR.

between male and female patients. The viral load for analysis was categorized into two levels: low level ($\leq 8 \times 10^5$ IU/ml) and high level ($>8 \times 10^5$ IU/ml). The response rate to treatment varied as the viral load increased. Patients with a pretreatment viral load of $\leq 8 \times 10^5$ IU/ml were compared to those with a pretreatment viral load of $>8 \times 10^5$ IU/ml: 83.5% vs. 46.8%, $p < 0.0001$. RVR had a high predictive value for achieving SVR; 83.5% (293/351) of patients with undetectable HCV RNA at week 4 had undetectable HCV RNA at follow-up (24 weeks after treatment completion). Most of the patients ($n = 363$) were in the raised ALT group. We did not observe a difference in SVR between the normal ALT group and the raised ALT group (74.2% vs. 74.9%).

Factors with significant associations in the univariate analysis were further analyzed by multivariate logistic regression. According to the multivariate logistic regression analysis, age ≤40 years (adjusted odds ratio (OR) 1.7, 95% confidence interval (CI) 1.036–2.916, $p < 0.001$), RVR (adjusted OR 6.32, 95% CI 3.79–10.55, $p < 0.001$), pretreatment viral load $\leq 8 \times 10^5$ IU/ml (adjusted OR 3.09, 95% CI 1.747–5.46, $p < 0.001$), and BMI ≤27 kg/m^2 (adjusted OR 1.73, 95% CI 0.98–3.124, $p = 0.05$) were independently associated with achieving SVR (Figure 4).

3.2. Adverse events

The incidence of side effects in the 16-week treatment group was similar to that in the 24-week treatment group. Adverse events in the two groups included fatigue, headache, and an influenza-like syndrome. Most of the patients experienced fever because interferon raises the body temperature. Fortunately these symptoms tend to lessen after the first few weeks of therapy. Hemoglobin levels decreased in the first few weeks and returned to normal within a few weeks of completion of treatment. However alopecia cases were seen only in the 24-week treatment group (Figure 4).

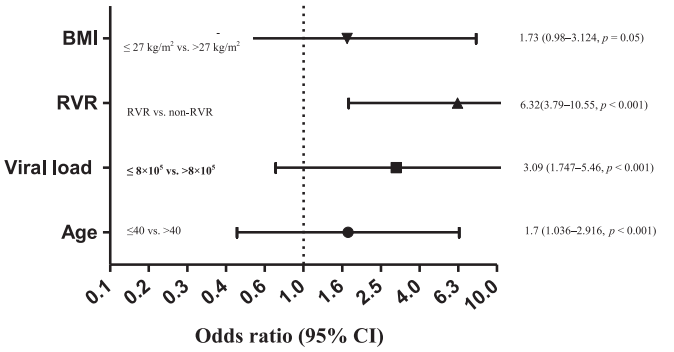

Figure 4. Multiple logistic regression model to predict SVR.

4. Discussion

The gold standard treatment for chronic hepatitis C (CHC) patients is PEG IFN in combination with ribavirin. Being expensive and requiring a long treatment duration, this therapy imposes a huge economic burden on the economy of a developing country such as Pakistan. A significant proportion of the Pakistani population (approximately 10 million) is infected with this virus.[12] In Pakistan, HCV genotype 3 is highly prevalent.[13] The standard therapy for HCV genotypes 2 and 3 is 24 weeks of PEG IFN in combination with ribavirin. For these reasons it is important to tailor the duration of treatment. RVR may be an important landmark for determining the duration and outcome of treatment.[14–16] The assessment of Dalgard and Mangia is in favor of 16 weeks of therapy for patients with HCV genotype 2 infection,[17] however there is no such recommendation for genotype 3. In this study, we showed that a shorter course of 16 weeks of PEG IFN alfa-2a and ribavirin 400 mg twice a day is as effective as a standard 24-week course in the Pakistani population infected with chronic HCV genotype 3, who achieved RVR at week 4.

In this study, the observed overall SVR to PEG IFN alfa-2a plus ribavirin therapy was 74.8%. This is higher when compared with the response rate predicted by Rumi et al. (65%) and that predicted by Shiffman et al. (70%).[18,19] A number of viral and host factors have been found to modulate the response to antiviral treatment. In agreement with previous studies,[20,21] the multivariate analysis revealed younger age, lower baseline viral loads, lower BMI, and RVR to be independent predictors of SVR.

Numerous studies have documented that females respond better to IFN therapy than males, but our study showed that the overall rate of successful responses to therapeutic regimens was higher in males; however the difference was not statistically significant (female 74.2% vs. male 75.5%, $p = 0.75$). Our study further showed that among females, age was also an important factor with regard to therapy response. Women aged ≤40 years had a better response to standard treatment compared to women aged >40 years (≤40 years vs. > 40 years, 84.7% vs. 65.2%). Hayashi correlated estrogen hormone with a better response in younger women and strongly suggest that estrogen may enhance the efficacy of IFN therapy.[22] Moreover some reports have described that aging leads to a decline in the ability of the immune system to protect the host from pathogens due to a reduction in naïve T-cells.[23,24]

Several studies have revealed that there is an inverse relationship between pretreatment viral load and SVR.[25,26] Our data support this finding to some extent, because there was a significantly lower risk of relapse of SVR after 16 weeks among patients with a pretreatment viral load $\leq 8 \times 10^5$ IU/ml compared to those with a high viral load (3.8 vs. 24.3, $p = 0.001$).

In our study 351 (76.3%) patients with HCV genotype 3 attained RVR, while 109 did not achieve RVR. The failure of attaining RVR may be due to replication of drug resistance variants, which may develop by selective pressure of drug therapy.[27] Among RVR patients, the risk of viral relapse was 16.5%, and 83.5% of them eradicated the virus. In agreement with Puoti et al.,[28] who reported rates of RVR and SVR in HCV genotype 3 patients of 64% and 82%, respectively, our study also showed the SVR rate achieved in RVR patients to be higher as compared to the rate achieved in patients who did not have RVR (88.3% vs. 63.6%, $p < 0.001$), showing that RVR is a strong predictor of SVR.[29] It also suggests that the week-4 virological response is a useful guide for treatment duration in HCV genotype 3 infection. Shortening the treatment period for chronic HCV infection is of major importance because this will reduce the costs for both patients and society.

Several studies have revealed that a shorter treatment duration in patients with HCV genotypes 2 and 3 results in a higher relapse rate than in patients treated for 24 weeks.[18,19] In contrast to these studies, our results revealed that SVR was almost equal among patients who achieved RVR with a short treatment duration and with a 24-week duration (82.2% vs. 86%). These data are consistent with data reported by other authors[6,7] and suggest that a short treatment regimen is as effective as a 24-week regimen for patients with HCV genotypes 2 and 3, especially those with RVR. Further prospective studies with larger numbers of patients are necessary to assess whether the standard treatment duration (24 weeks) and the short treatment duration (16 weeks) produce equal outcomes in genotype 3 patients. This study will also help to establish guidelines for short treatment regimens for genotype 3-infected patients who have the ability to achieve SVR.

In conclusion, monitoring the viral response in treatment-naïve patients with chronic hepatitis C may be useful to individualize treatment duration. Patients with a high sensitivity to PEG IFN showing rapid decreases in viral kinetics may be selected and safely treated for a shorter period of time than in the past. Shortening the treatment duration to 16 weeks may be sufficient in Pakistani patients with HCV genotype 3 who have achieved RVR, have a low BMI, and who are younger in age.

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Conflict of interest: No conflict of interest.

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