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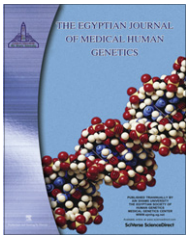

ORIGINAL ARTICLE

Virologic response at week 8 of combined treatment as a predictor of sustained virologic response in non rapid virologic response, chronic HCV genotype 4 infected patients

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KEYWORDS

Week 8;
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Abstract Optimization of interferon-based treatment regimens remains an important goal as pegylated interferon is likely to remain the backbone of chronic HCV treatment in the foreseeable future.

The objective of the current study was to evaluate virological response at week 8 of combined treatment as a predictor of sustained virologic response (SVR) in non rapid virologic response (RVR), chronic HCV genotype 4 infected patients.

A total of 38 patients with chronic HCV genotype 4 infection were enrolled in the study. All patients received a combination of pegylated interferon α-2a plus ribavirin. Virological response at week 8 of combined treatment was evaluated as a predictor of SVR.

Week 8 response was more sensitive but less specific than RVR in predicting SVR, in non RVR patients (24 patients), week 8 response had a sensitivity of 45.5% and a specificity of 76.9% for predicting SVR.

In conclusion: In non RVR patients, measurement of HCV RNA at week 8 is an optimal time to identify those who are not going to benefit from pegylated interferon and ribavirin combination therapy.

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1. Introduction

HCV genotype 4 (HCV-4) is common in the Middle East and in Africa, where it is responsible for more than 80% of HCV infections, and has recently spread to several European countries [1]. Egypt has the highest prevalence of HCV worldwide (15%) [2] and the highest prevalence of HCV-4, which is responsible for almost 90% of infections and is considered a major cause of chronic hepatitis, liver cirrhosis, hepatocellular carcinoma, and liver transplantation in the country [3].

The combination of pegylated interferon plus ribavirin is the treatment of choice for patients with chronic hepatitis C [4]. Optimization of interferon-based treatment regimens remains an important goal as pegylated interferon is likely to remain the backbone of treatment in the foreseeable future.

The rate and extent of virologic response to combination therapy in patients infected with hepatitis C virus (HCV) genotype 1 or 4 is highly variable [5,6]. In patients with chronic hepatitis C, the on-treatment response at weeks 4 and 12 of pegylated interferon plus ribavirin combination therapy may be used to predict the probability of sustained virologic response (SVR). Patients achieving rapid virologic response (RVR) (HCV RNA < 50 IU/mL at week 4) have a high rate of SVR, irrespective of HCV genotype [7].

The standard definition of an early virologic response (EVR) is undetectable HCV RNA (< 50 IU/mL) by qualitative PCR or a $\geqslant 2$ log drop in HCV RNA at week 12 by quantitative PCR [6]. However, the positive predictive value of an EVR is not high enough to be a useful clinical predictor of SVR [8].

To our knowledge, the value of virological response at week 8 of combined treatment as a predictor of SVR in non RVR chronic HCV genotype 4 infected patients has not been well evaluated.

The objective of the current study was to evaluate virological response at week 8 of combined treatment as a predictor of SVR in non RVR chronic HCV genotype 4 infected patients.

2. Patients and methods

A total of 38 treatment naïve patients with chronic HCV genotype 4 infection were enrolled in the study (36 males and 2 females with ages ranging from 32 to 48 years "mean = 40").

All patients were fulfilling the criteria for combined treatment with pegylated interferon α-2a and ribavirin.

All patients were subjected to the following:

- History taking, thorough clinical examination including fundus examination, laboratory investigations including: fasting and post prandial blood glucose level, liver function tests, Alpha-fetoprotein, prothrombin time and INR, renal function tests, serum ceruloplasmin, complete blood count, free T3, free T4, TSH (Thyroid Stimulating Hormone), ANA (Antinuclear Antibody), HIV (Human Immune Deficiency Virus) antibody and hepatitis C virus antibody using ELISA (Enzyme Linked Immune Sorbant Assay) technique.
- Hepatitis B Virus (HBV) markers (HBsAg, HBsAb, HBcAb, HBeAg and HBeAb).
- HCV RNA in serum, both quantitative and qualitative using Polymerase Chain Reaction (PCR):
- Automated PCR (using Cobas Ammplicor HCVv2.0, Roche molecular system) was used for qualitative HCV RNA detection.
- Manual PCR (using Cobas Ammplicor HCVv2.0, Roche molecular system) was used for quantifying HCV RNA.
- Interpretation of viremia:
  < 200.000 IU/ml: low viremia.

  200.000–2000.000 IU/ml: moderate viremia.
  > 2000.000 IU/ml: high viremia.
- HCV genotyping using INNO-LIPA HCVII test (INNO-LiPA HCV II, Innogenetics, Ghent, Belgium), this test is based on reverse hybridization of 5′ untranslated region PCR amplification product [9].
- Abdominal ultrasonography (Aloka SSD620, Japan) using 3.5 MHz convex probe.
- Fibroscan was done for all patients. Fibroscan is designed for non invasive assessment of liver fibrosis and is based on elastometry (or one dimensional transient elastography), the harder the tissue, the faster the shear wave propagates [10].
- 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 5 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 are expressed in kilopascal (kPa).
- The values used to correlate elastometry with METAVIR scoring system are the followings: < 7.1 kPa for F0–1, 7.1–9.4 kPa for F2, 9.5–12.5 kPa for F3 and > 12.5 kPa for F4 [11].
- 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).
- This study was approved by the local ethical committee of the Ain Shams University hospitals and a written consent was obtained from each individual before participation in the study.

Exclusion criteria:

1. Patients with decompensated cirrhosis.
2. Patients with hepatocellular carcinoma.
3. Patients with diabetes mellitus.
4. Patients with HBV infection.
5. Current pregnancy or breastfeeding.
6. Prior or current anti viral therapies.
7. Regular or excessive alcohol consumption.
8. 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.
9. Morbid obesity (BMI $\geqslant 40$).
10. Current intravenous drug abuse.
11. Neutropenia ($< 1500/mm^3$).

12. Thrombocytopenia ($< 90{,}000/mm^3$).
13. Serum creatinine more than 1.5 times the upper limit of normal value.
14. Severe cardiac, pulmonary, retinal, thyroid, or psychiatric disorders.
15. HIV infection.

3. Statistical methods

The data were collected, coded and entered to a personal computer (P.C.) IBM compatible 2.6 GHz. The data were analyzed with the program statistical package for social science (SPSS) under windows version 11.0.1.

4. Calculation of sensitivity and specificity

Sensitivity = TP/TP + FN.
Specificity = TN/TN + FP.
Positive predictive value (PPV) = TP/TP + FP.
Negative predictive value (NPV) = TN/TN + FN.
Accuracy = TP + TN/All cases.
TN = true negative.
TP = true positive.
FN = false negative.
FP = false positive.

5. Results

A total of 38 patients with chronic HCV genotype 4 infection were enrolled in the study (36 males and 2 females with ages ranging from 32 to 48 "mean = 40").

All patients had pretreatment moderate viremia with HCV RNA ranging from 200.000 to 2000.000 IU/ml.

Twenty-one patients had a pretreatment fibroscan score ranging from 7.1 to 9.4 kPa (F2) and the remaining 17 patients had a pretreatment fibroscan score ranging from 9.5 to 12.5 kPa (F3).

All patients received a combination of pegylated interferon α-2a plus ribavirin.

Virological response at week 8 of combined treatment was evaluated as a predictor of SVR (response after 24 weeks of discontinuation of treatment) in thepatients who failed to achieve RVR (week 4 response).

Of the 38 patients, 14 (36.8%) patients achieved RVR and 21 patients (55.2%) achieved SVR (Table 1).

10 out of 14 RVR patients achieved SVR (71.4% of RVR patients) and 11 out of 24 non RVR patients achieved SVR (45.8% of non RVR patients) (Table 1).

Of the RVR patients, 13 out of 14 patients had an undetectable HCV RNA at week 8 of therapy and of these 13 patients, only 10 patients achieved SVR.

Twenty-four patients failed to achieve RVR. Only 8 of these patients (33.3% of non RVR patients) had an undetectable HCV RNA at week 8 of therapy and of these 8 patients, only 5 patients (62.8% of non RVR patients who had an undetectable HCV RNA at week 8 of therapy) achieved SVR (Table 3).

Sixteen non RVR patients (66.6% of non RVR patients) had detectable HCV RNA at week 8 of therapy and only 6 out of these 16 patients (37.5% of non RVR patients who had detectable HCV RNA at week 8 of therapy) achieved SVR (Table 3).

Regarding EVR in non RVR patients, only 14 patients (58.3% of non RVR patients) achieved EVR and of these, only 9 patients (62.5% of non RVR patients who achieved EVR) achieved SVR. Among the 10 patients who failed to achieve

Table 1 Comparison between RVR and SVR.

RVR	SVR			
	Responders $N = 21$		Non response $N = 17$	
	No.	%	No.	%
Responders $N = 14$	10 (TP)	47.6	4 (FP)	23.5
Non responders $N = 24$	11 (FN)	45.8	13 (TN)	76.5

SVR: sustained virologic response.
RVR: rapid virologic response.
TN = true negative, TP = true positive.
FN = false negative, FP = false positive.
Sensitivity = 47.6%, Specificity = 76.5%.
Positive predictive value (PPV) = 71.4%, negative predictive value NPV = 54.2%.
Accuracy = 60.5%.

Table 2 Comparison between week 8 response and SVR.

Week 8	SVR			
	Responders $N = 21$		Non responders $N = 17$	
	No.	%	No.	%
Responders $N = 21$	15 (TP)	71.4	6 (FP)	35.3
Non responders $N = 17$	6 (FN)	28.6	11 (TN)	64.7

Sensitivity = 71.4%, specificity = 64.7%.
PPV = 71.4%, NPV = 64.7%.
Accuracy = 68.4%.

Table 3 Comparison between week 8 response and SVR among non RVR patients.

Week8	SVR			
	Responders $N = 11$		Non responders $N = 13$	
	No.	%	No.	%
Responders $N = 8$	5 (TP)	45.5	3 (FP)	23.1
Non responders $N = 16$	6 (FN)	54.5	10 (TN)	76.9

Sensitivity = 45.5%, specificity = 76.9%.
PPV = 62.5%, NPV = 62.5%.
Accuracy = 62.5%.

Table 4 Comparison between EVR and SVR among non RVR patients.

EVR	SVR			
	Responders $N = 11$		Non responders $N = 13$	
	No.	%	No.	%
Responders $N = 14$	9 (TP)	65.2	5 (FP)	35.7
Non responders $N = 10$	2 (FN)	20.0	8 (TN)	80.0

EVR: early virologic response.
Sensitivity = 81%, specificity = 61.5%.
PPV = 64.2%, NPV = 80.0%.
Accuracy = 70.8%.

EVR (41.6% of non RVR patients), only 2 patients (20.0% of non RVR patients who failed to achieve EVR) achieved SVR (Table 4).

Week 8 response was more sensitive (71.4% vs. 47.6%) but less specific (64.7 vs. 76.5%) than RVR in predicting SVR (Tables 1 and 2).

Both RVR and week 8 responses had the same PPV (71.4%) but the NPV of week 8 response was higher than that of RVR (64.7% vs. 54.2%) (Tables 1 and 2).

In non RVR patients, week 8 response was less sensitive (45.5% vs. 81%) but more specific (76.9% vs. 61.5%) than EVR in predicting SVR (Tables 3 and 4).

The positive and negative predictive values of week 8 response were lower than the predictive values of EVR (62.5% vs. 64.2% and 62.5% vs. 80%, respectively) (Tables 3 and 4).

6. Discussion

The management strategies for patients infected with HCV-4 are not yet well established. The limited distribution of this genotype in the Western countries and subsequently the small percentage of HCV-4 patients in major multicenter HCV therapeutic trials may in part explain this phenomenon [12].

The response to antiviral therapy in HCV-infected patients is heterogeneous and, despite increases in SVR rates, treatment outcomes with peg-interferon α-2a plus ribavirin are not optimal in certain patient populations and might still be improved [13,14].

While some authors found that both RVR and complete early virologic response are associated with the achievement of SVR in patients with (chronic hepatitis C) CHC, others found the positive predictive value of an EVR not high enough to be a useful clinical predictor of SVR [8].

Early identification of those patients who are unlikely to achieve SVR may help to reduce unnecessary healthcare expenses and limit the side-effects associated with drug exposure.

The objective of the current study was to evaluate virological response at week 8 of combined treatment as a predictor of SVR in non RVR chronic HCV genotype 4 infected patients.

In the current study, 36.8% of patients achieved RVR and 55.2% achieved SVR. This result goes in agreement with a retrospective analysis of SVR rates which was done among 205 naive French and Egyptian HCV-4 patients and revealed a better overall SVR in Egyptians than in Europeans (54.9% vs. 40.3%) treated with PEG-IFN and ribavirin [15].

In RVR patients, SVR was 71%. In contrast, only 45.8% of non RVR patients achieved SVR. These results confirm other reports which found SVR rates to be highest among patients who achieve RVR [16,17].

Regarding EVR in non RVR patients, only 58.3% of patients achieved EVR and of these, 62.5% achieved SVR. 41.6% of patients failed to achieve EVR and 20.0% of these patients achieved SVR.

In comparison EVR rate that was found in the present study with EVR rate reported by Ferenci and co-workers [18], a higher EVR was observed.

The fact that EVR was evaluated only in non RVR patients may in part explain this higher rate. Also differences in the ethnicity, number of patients included in each study, viral genotype and/or subtype and baseline viral load make any direct comparison with the present study difficult.

In non RVR patients, only 33.3% of patients had an undetectable HCV RNA at week 8 of treatment and 62.5% of these patients achieved SVR. 66.6% non RVR patients had detectable HCV RNA at week 8 of therapy and of these patients, only 37.5% achieved SVR.

The comparable SVR rates in relation to week 8 response and EVR encouraged incorporation of on-treatment virological response at week 8 into the treatment algorithm for patients with genotype 4 infection who fails to achieve RVR to provide clinicians with a useful tool to identify patients who are unlikely to achieve SVR.

In accordance with this conclusion, the present study found that week 8 response was more specific (76.9% vs. 61.5%) than EVR in predicting SVR. This result also highlights the value of week 8 response in identifying patients who are less likely to achieve SVR.

Despite the relatively high specificity of week 8 response for the prediction of SVR in non RVR patients, the NPV of this test was lower than the NPV of EVR that was reported not only by the present study but also by other reports [19,20].

The NPV for week 8 response reported by the current study was measured only for non RVR patients. In contrast, the NPV of EVR reported by other studies was measured for all patients irrespective of week 4 response.

This study was limited by the relatively small sample size, reducing the statistical power to evaluate virological response at week 8 of combined treatment as a predictor of SVR in non RVR chronic HCV genotype 4 infected patients. However, the result of the study encourages the conduction of further studies on a larger scale of patients.

7. Conclusion

In non RVR patients, measurement of HCV RNA at week 8 is an optimal time to identify those who are unlikely to benefit from pegylated interferon and ribavirin combination therapy.

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