Original Article

Prediction of sustained virologic responses to combination therapy of pegylated interferon-α and ribavirin in patients with chronic hepatitis C infection

Mona H. Ismail

Department of Internal Medicine, Division of Gastroenterology, University of Dammam, College of Medicine, King Fahd Hospital of the University, Al-Khobar, Saudi Arabia

Address for correspondence: Dr. Mona H. Ismail, Consultant Hepatologist, Assistant Professor of Medicine, Department of Internal Medicine, Division of Gastroenterology, University of Dammam, College of Medicine, King Fahd Hospital of the University, PO Box 40149, Al-Khobar-31952, Saudi Arabia. E-mail: mismail.md@gmail.com

ABSTRACT

Background and Aim: Hepatitis C virus (HCV) infection is a major health problem worldwide. Genotype-4 is the most common genotype in Saudi Arabia. The response to treatment with pegylated interferon-α combined with ribavirin in chronic HCV infection varies. This study aimed at investigating the pre- and on-treatment predictors of sustained virologic response (SVR) in patients with chronic hepatitis C (CHC) infection. **Patients and Methods**: Clinical data of 48 patients with CHC treated with standard HCV antiviral combination therapy, between January 2005 and December 2010, at a Saudi University hospital, were retrospectively reviewed for age, sex, body mass index, liver enzymes, HCV-RNA viral load, liver biopsy, and response to treatment. The primary end point was SVR defined as undetectable HCV-RNA by polymerase chain reaction (PCR) 24 weeks after the end of treatment. Univariable logistic regression was used to explore the association between the different variables and SVR. These independent predictors of SVR were then analyzed with multivariable logistic regression analysis. **Results:** Of the 48 treated patients, 25 (52%) were females and 27 (56%) were Saudi. The mean age was 43 years (43 ± 10 years). Twenty-four (50%) had genotype-4, and 26 (54%) had liver biopsy. The overall SVR rate was 75% (36/48) and was 83.3% (20/24) among genotype-4 patients. Baseline factors associated with SVR identified by univariate logistic regression were genotype-4 and early viral response (EVR), defined as a drop of ≥2 log in serum HCV viral load after 12 weeks of initiation of combination therapy (P = 0.001). However, in stepwise regression analysis, the independent factor associated with the effect of antiviral therapy was genotype-4. When on-treatment variables were included, EVR (P = 0.003) and low baseline viral load (P = 0.048) were highly predictive of SVR. **Conclusions:** Of our HCV-treated patients, 75% had SVR. HCV genotype-4, EVR, and low baseline viral load were predictive of SVR.

Key words: Chronic hepatitis C, Saudi, sustained virologic response, treatment response predictors

INTRODUCTION

Hepatitis C virus (HCV) infects an estimated 170 million persons worldwide.[1] HCV infection is a major health problem in most parts of the world, as it can lead to chronic active hepatitis, liver cirrhosis, and hepatocellular carcinoma.[2] If untreated, chronic HCV infection can lead to significant morbidity and mortality.[3,4] Hepatitis C genotype-4 is the most common type in the Middle East, including Saudi Arabia and Africa.[5,6] The preliminary treatment reports with conventional interferon monotherapy had yielded disappointing sustained viral response rate of 10%–15%.[7] Since then, significant advances have been made in the treatment of HCV using pegylated interferon α-2a or α-2b plus ribavirin combination therapy. Sustained virologic response (SVR) rates > 50% have been reported with the use of combination therapies.[8] The ability to accurately predict the response of HCV patients to antiviral therapy is of great interest. Host and viral factors, such as HCV genotype, baseline viral load, fibrosis, body weight, and age, influence the response to therapy and can help predict treatment outcomes.[9] Once treatment is initiated,

Access this article online	
Quick Response Code:	Website: www.jfcmonline.com
	DOI: 10.4103/2230-8229.108182

on-treatment markers of response can further aid in predicting treatment outcomes. These markers include rapid virologic response (RVR, undetectable HCV-RNA at week 4 of therapy), early virologic response (EVR, undetectable HCV-RNA or ≥2 $\log_{10}$ decrease in HCV-RNA level from baseline at week 12 of therapy).[10] They can be assessed before therapy is started (pretreatment predictors) or during therapy (on-treatment predictors). Preferably, the on-treatment predictors should be available early in the treatment course so that patients who are unlikely to respond can have their treatment stopped and those who are likely to respond are encouraged to complete therapy.

The predictors of response to genotype-4 are not well represented in the large registration trials of antiviral therapy because most of the data were on genotype-1.[11] Currently, this gap in medical knowledge has been largely filled by investigators from Saudi Arabia, Egypt, and Kuwait, where genotype-4 is predominant.[12-14] Data on predictors of response to therapy are limited and there is, therefore, a need for further studies. Thus, the aims of this study were to assess SVR in patients with CHC infection and to assess pre- and on-treatment predictors of response.

MATERIALS AND METHODS

Patient population

Data from 48 patients with chronic hepatitis C treated at King Fahd Hospital of the University, Al-Khobar, between January 2005 and December 2010 were analyzed. The following conditions were excluded: coinfection with hepatitis B or human immunodeficiency viruses, active substance abuse, autoimmune hepatitis, hemochromatosis, α1-antitrypsin deficiency, Wilson's disease, and hepatic decompensation. Patients with serum creatinine above 1.5 mg/dL, absolute neutrophil count (ANC) below 750/μL, platelet count below 50,000/μL, or hemoglobin below 10 g/dL at baseline were excluded from the study. None of our patients consumed alcohol.

Clinical and laboratory assessment

Our study included patients with confirmed diagnosis of CHC by detectable anti-HCV (ELISA III), detectable HCV-RNA in serum within a month before the beginning of the treatment schedule, normal or elevated alanine aminotransferase level (ALT) (>40 IU/L and <400 IU/L), and/or liver biopsy indicating chronic hepatitis within 6 months before treatment. Patients' demographic and clinical data were obtained by a careful review of their hospital charts and electronic records. Each patient's age, gender, routine laboratory tests (complete blood count, biochemical tests), risk factors for contracting HCV infection, treatment side effects were documented on a data extraction sheet. All patients were clinically, hematologically, and biochemically evaluated at weeks 4, 12, 24, 48, and 72 of treatment follow-up or as needed.

Virologic assessment

Serum HCV-RNA levels and HCV genotype were measured using an automated extraction system (Cobas Amplicor) Abbott Real Time M2000 (RT-PCR technology) with a HCV-RNA detection rate range of 30–100,000,000 IU/mL. An Internal Control is included in the assays to monitor any possible amplification inhibitors. During the treatment course, serum HCV-RNA level was measured at treatment weeks 4, 12, 24, and 48, and 24 weeks after the end of treatment.

Definitions

The following definitions were used to assess the collected data:

Rapid viral response was defined as undetectable serum HCV RNA after 4 weeks of initiation of pegylated interferon and ribavirin combination therapy.

Early viral response was defined as ≥2 log decline in serum HCV-RNA level from baseline or undetectable HCV-RNA in serum after 12 weeks of initiation of pegylated interferon and ribavirin combination therapy.

End of treatment response was defined as undetectable serum HCV-RNA at the end of treatment.

Sustained viral response was defined as undetectable HCV RNA 24 weeks after the end of full course of pegylated interferon and ribavirin combination therapy.

Liver histology

Liver biopsy was performed at baseline, in chronic HCV patients infected with genotypes 1 or 4 only, by an 18-gauge Monopty liver biopsy (Bard Technologies, Covington, GA, USA) needles. Necroinflammation and fibrosis were assessed using the Metavir score.[15] Steatosis was assessed as the percentage of hepatocytes containing macrovesicular fat droplets. It was graded as 0 [absent (<5%)], 1 [moderate (5%–30%)], and 2 [severe (>30%)]. Patients with genotypes 1 or 4 who declined to have a liver biopsy had the option of an alternative noninvasive liver fibrosis test, such as FiboTest-ActiTest® (Biopredictive, France).

Treatment regimen

The patients were treated either with pegylated interferon-alpha 2a (PEGASYS, 180 μg per week) or with weight-based dosing of pegylated interferon-alpha 2b (PEG-INTRON, 1.5 μg/kg per week) plus ribavirin (1000–1200 mg/day for body weight <75 or ≥75 kg, respectively). Patients with genotype 2 or 3 were treated for 24 weeks, whereas those with genotypes 1 and 4 were treated for 48 weeks.

Treatment was stopped at week 24 if serum HCV-RNA was still detectable. Patients with detectable serum HCV-RNA 6 months after completion of treatment were characterized as nonresponders in the analyses. To maintain the starting dose combination therapy, the patients were given erythropoietin and granulocyte-colony stimulating factor if they developed treatment-induced anemia (<10 g/dL) or neutropenia (ANC below 750/μL), respectively.

Statistical analysis

Descriptive data are provided as percentages, mean ± SD for normally distributed data or median [interquartile range (IQR)] for non-normal data. Quantitative data were analyzed by Student's *t* test for normally distributed data and by Mann–Whitney *U* test for non-normally distributed data. Variables achieving statistical significance in univariate analysis were included in stepwise binary logistic regression analysis using a backward selection method. The magnitude of these associations is reported as the odds ratio (OR with 95% CI). *P* values < 0.05 were considered significant. All analyses were conducted with the PASW 18 software (IBM-SPSS Inc).

This study was conducted in accordance with the Helsinki Declaration and was approved by the ethics committee of the University of Dammam.

RESULTS

Baseline and clinical characteristics

Of the 48 patients included in this study, 25 (52%) were women and 23 (48%) were men; their mean age was 43 ± 10 years. Baseline characteristics of these 48 patients are presented in Table 1. Twenty-seven percent were chronically infected with HCV genotype-1, 8.3% genotype-2, 14.6% genotype-3, and 50% genotype-4. The median pretreatment quantitative HCV-PCR level was 700,000 IU/L (IQR: 238,000–700,000). Twenty-six (54%) had liver biopsies, which showed grade 0–1 in 9 (34.5%) and grade 2–3 in 17 (65.5%). Seventeen patients (46%) had fibrosis between stage 0–2, whereas 7 (27%) had advanced fibrosis and 2 were cirrhotic (8%). The mean hemoglobin level was 13.8 ± 1.7 g/dL; ALT was elevated (≥40 IU/L) in 42 (88%). Forty-two patients (87.5%) were treatment naïve. Thirty-nine (81%) were treated with Peginterferon α-2a and 9 (19%) with Peginterferon α-2b.

Of the 48 patients, 30% had a history of prior surgery or blood transfusion, 6% a history of dental treatment, 4% had needle stick injury, and the remaining 60% were incidentally detected to be HCV positive.

All patients experienced treatment related side effects of mainly flu-like illness. One patient with genotype-3

Table 1: Patients' characteristics at baseline and response to treatment

	Patients with chronic hepatitis C (N = 48)
Gender	
Female	25 (52.0%)
Nationality	
Saudi	27 (56.0%)
Age (years)	43 ± 10.0
<40	15 (31.2%)
≥40	33 (68.8%)
BMI (kg/m^2)	29.3 ± 6.2
<30	25 (52.1%)
≥30	14 (29.2%)
Missing	9 (18.8%)
Type 2 diabetic	
Present	6 (12.5%)
ALT (IU/L) median (IQR)	59.0 (48.0-80.75)
ALT ≥ 40 IU/L	42 (87.5%)
Platelet count × 10^3/mmc	228± 81.0
Hemoglobin (g/dL)	13.8 ± 1.7
HCV-RNA level (IU/L) – (median (IQR)	700,000 (283,000–700,000)
HCV-RNA level	
<5 × 10^5 (i.e., 500,000 IU/L)	19 (39.6%)
≥5 × 10^5	29 (60.4%)
HCV genotype	
Type 1	13 (27.1%)
Type 2	4 (08.3%)
Type 3	7 (14.6%)
Type 4	24 (50.0%)
Liver biopsy	
Yes	26 (54.0%)
Metavir fibrosis score	
F0	5 (19%)
F1	7 (27%)
F2	5 (19%)
F3	7 (27%)
F4	2 (8%)
Metavir inflammatory score	
A0	3 (11.5%)
A1	6 (23%)
A2	7 (27%)
A3	10 (38.5%)
Steatosis score	
0	9 (34%)
1	14 (54%)
2	2 (8%)
3	1 (4%)
Treatment naïve	
Yes/no	42/6 (87.5%)
Virologic response to treatment	
Sustained response	36 (75%)
End of treatment response with relapse	12 (10%)
Nonresponse	7 (15%)

BMI, body mass index; ALT,alanine aminotrasnferase; IQR, interquartile range; HCV-RNA, hepatitis C virus-RNA. Data are expressed as mean ± SD (range) unless otherwise stated

developed major side effects (suicide attempt after discontinuing antidepressant therapy) and pegylated interferon was discontinued for 2 weeks, yet the virus was cleared . Eleven (23%) patients developed neutropenia and required hematopoietic support. Other reported side effects were thyroid dysfunction (hypothyroidism or hyperthyroidism), hair loss, anorexia, and itching. The remainder of the patients completed treatment without a reduction of the dose or a discontinuation.

Response to treatment

The overall SVR rate was 75% (36/48) and among genotype-4 patients was 83.3% (20/24). Of the remaining 12, 5 (10.4%) were primary nonresponders and 7 (14.6%) relapsers. The SVR rates among different genotypes are summarized in Figure 1. RVR was achieved in 12 (25%) and EVR in 41 patients (85%). Two cirrhotic patients with genotype-4 had an SVR rate of 50%. Hepatic fibrosis showed no difference in SVR. Similarly, younger age (<40 years) and baseline serum alanine aminotransferase (ALT) were also not associated with SVR.

Factors predictive of SVR

On univariate logistic regression analysis, low viral load (<500,000 IU/L) (P = 0.078), genotypes-2 and -3 (P = 0.039), genotype-4 (P = 0.024), RVR (P = 0.086), and EVR (P = 0.001) were predictive of SVR. In contrast, age (P = 0.372), elevated serum ALT (P = 0.148), gender (P = 0.407), and lower body mass index (BMI) (≤30 kg/ m^2) (P = 0.657) were not predictive of SVR [Table 2]. On multivariate logistic regression analysis, including the baseline predictors outlined in the methods section, only genotype-4 (P = 0.026) remained in the model predictive of SVR. When on-treatment variables were included, EVR (P = 0.048) and baseline viral load (P = 0.003) were selected as independent predictors [Table 3].

DISCUSSION

The goal of treatment in patients with chronic HCV infection is to eradicate the virus, which is characterized by the attainment of an SVR. Treatment of HCV patients with the combination therapy in our study was associated

Table 2: Factors associated with sustained virologic response in 48 patients with hepatitis C virus: univariate logistic regression analysis

Variable	n	SVR (%)	Odds ratio (95% CI)	*P* value
Gender				
Male	23	16 (69.6)	1	
Female	25	20 (80.0)	1.75 (0.47–6.57)	0.407
Age (years)				
<40	15	10 (66.7)	1	
≥40	33	26 (78.8)	1.86 (0.48–7.23)	0.372
BMI (kg/m^2)				
<30	25	20 (80.0)	1	
≥30	14	12 (85.7)	1.50 (0.25–8.98)	0.657
Type 2 diabetic				
Absent	42	31 (73.8)	1	
Present	06	5 (83.3)	1.77 (0.19–16.91)	0.618
ALT (in IU/L)				
< 40	06	3 (50.0)	1	
≥ 40	42	33 (78.6)	3.67 (0.63–21.35)	0.148
HCV-RNA level (in IU/L)				
<500,000	19	17 (89.5)	1	
≥500,000	29	19 (65.5)	0.22 (0.04–1.17)	0.078
HCV genotype				
1	13	6 (46.2)	1	
2-3	11	10 (90.9)	11.67 (1.13–119.55)	0.039
4	24	20 (83.3)	5.83 (1.26–26.95)	0.024
Virologic response				
RVR				
No	36	24 (66.7)	1	
Yes	12	12 (100.0)	12.76* (0.70–233.60)	0.086
EVR				
No	10	3 (30.0)	1	
Yes	38	33 (86.8)	15.40 (2.97–79.98)	0.001

BMI, body mass index; EVR, early virologic response; HCV-RNA, hepatitis C virus RNA; RVR, rapid virologic response; ALT, alanine aminotransferase ; SVR, sustained virologic response. *Corrected odds ratio for zero-cell count

Table 3: Factors associated with sustained virologic response in 48 patients with hepatitis C virus: multiple logistic regression analysis

A: "Baseline predictors"		
Variable	**Adjusted OR (95% CI)**	***P* value**
Baseline HCV-RNA		
<500,000	1.00	
≥500,000	0.23 (0.04–1.37)	0.107
HCV genotype		
1	1.00	
2-3	10.16 (0.93–111.16)	0.057
4	6.17 (1.24–30.75)	0.026
B: "On-treatment predictors"		
Variable	**Adjusted OR (95% CI)**	***P* value**
Baseline HCV-RNA		
<500,000	1.00	
≥500,000	0.09 (0.01–0.98)	0.048
EVR		
No	1.00	
Yes	31.43 (3.30–299.77)	0.003

CI, confidence interval; EVR, early virologic response; HCV-RNA, hepatitis C virus-RNA; OR, odds ratio.
*Models A and B were without and with "on treatment predictors."

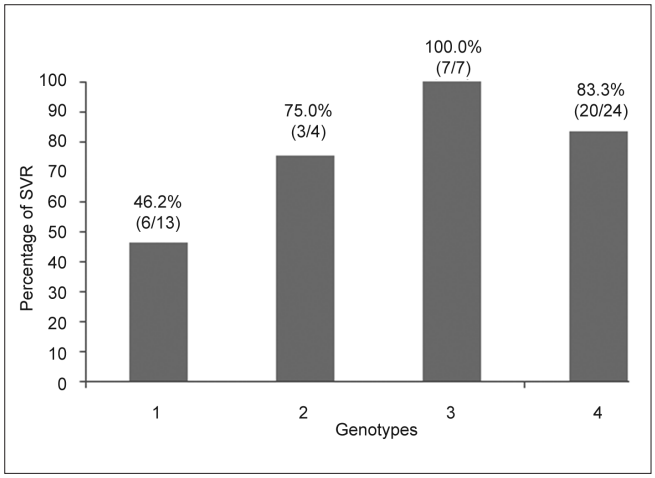

Figure 1: Sustained virologic response rates among different genotypes

with a high SVR rate of 75% in all treated patients and 83.3% in genotype-4 patients. This is likely to be due to the inclusion predominantly of patients who were motivated and adhered to treatment with favorable baseline characteristics, that is, treatment naïve patients (87.5%), predominance of ≤ F2 fibrosis (65%) as well as the use of hematopoietic support, which helped to avoid discontinuation of treatment or reduction in therapy doses. The treatment was tailored to initial treatment response and genotype. The SVR observed in the study is higher than that reported in previous studies, particularly for genotype-4.[12,16,17] In this study, low viral load (<500,000 IU/L), genotype-4, and EVR were predictive of SVR.

Gad *et al*.[14] reported that SVR rate was 54.8% in genotype-4. Furthermore, patients with severe fibrosis (F > 2) were half as likely to achieve SVR compared with those with mild fibrosis. In this study, liver fibrosis was not used as a predictor of response because of the small number of patients with available biopsy data.

It is well known that predictors of response serve as decision tools for treating physicians to help identify patients who are likely or unlikely to achieve SVR and, thus, reduce the risk of side effects and cost, and spare patients the disappointment of treatment failure.[1] Of the 5 baseline predictors for SVR originally described by Poynard *et al*,[18] we were only able to confirm low baseline viremia. This study demonstrates for the first time genotype-4 as an independent baseline predictor of SVR, which most likely is due to its predominance (50%) in our cohort. Our results are similar to those of previous studies [13,17,19] that identified low viral load, and EVR as independent positive predictors of an SVR.

Age, obesity, and gender were not confirmed as independent baseline predictors. Previous data suggested that obesity, defined as BMI > 30 kg/m^2, was a risk factor for nonresponse to antiviral therapy.[20,21] The mechanism whereby obesity may affect the antiviral response to treatment is not completely understood. BMI has been shown to correlate with the degree of steatosis seen in hepatitis C.[22]

Other studies[13,17] defined high viral load as HCV-RNA > 800,000 IU/mL. Backus *et al*. identified 5944 hepatitis C patients who were treated at Veterans Affairs Health Care with PEG-INF/ribavirin and found that patients with low viremia (500,000 IU/mL) were more likely to respond than patients with a high viral load.[23] Similarly, our study confirmed low viremia (500,000 IU/mL) and non-1 genotype as strong independent predictors of response to therapy.

Genome-wide association studies have recently identified single-nucleotide polymorphisms in the region of the IL28B gene on chromosome 19 that strongly predict treatment response in patients infected with HCV.[24] Patients with the good-response genotype can be expected to have a 70% likelihood of SVR with standard care of therapy. Similar results were seen with genotype-2/3.[25] Asselah *et al*,[26] recently studied IL28B polymorphism in 82 out of 164 HCV genotype-4 patients for response to treatment and found rs12979860 CC genotype associated with better response rate of 81.8%. Thus, incorporating IL28B genotyping into clinical practice may assist treating physicians in planning therapy for HCV infection. The

approval of two protease inhibitors for genotype-1[27,28] will further improve SVR rates as well as shorten therapy.

The main limitations of our study are primarily related to its small sample size and retrospective design. However, our study highlighted the importance of non-1 genotype, EVR and low viral load as positive predictive factors to attaining SVR in this population.

In conclusion, in the present study, sustained virologic response rates to pegylated interferon/ribavirin were 75% in the whole series, and 83.3% among genotype-4 patients. HCV genotype-4, EVR and low baseline viral load were independent positive predictors of an SVR in CHC patients.

REFERENCES

1. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med 2001;345:41-52.
2. Heintges T, Wands JR. Hepatitis C virus: Epidemiology and transmission. Hepatology 1997;26:521-6.
3. De Filippi F, Colombo M. Treatment of chronic hepatitis C. J Biol Regul Homeost Agents 2003;17:133-7.
4. Coverdale SA, Khan MH, Byth K, Lin R, Weltman M, George J, *et al*. Effects of interferon treatment response on liver complications of chronic hepatitis C: 9-year follow-up study. Am J Gastroenterol 2004;99:636-44.
5. McOmish F, Yap PL, Dow BC, Follett EA, Seed C, Keller AJ, *et al*. Geographical distribution of hepatitis C virus genotypes in blood donors: An international collaborative survey. J Clin Microbiol 1994;32:884-92.
6. al Faleh FZ, Huraib S, Sbeih F, al-Karawi M, al-Rashed R, al-Mofleh IA, *et al*. Hepatitis C virus genotypes in patients with chronic liver disease and haemodialysis patients from Saudi Arabia. J Viral Hepat 1995;2:293-6.
7. Abdo AA, Sanai FM. Predictors of sustained virologic response in hepatitis C genotype 4: Beyond the usual suspects. Ann Saudi Med 2009;29:1-3.
8. Dienstag JL, McHutchison JG. American Gastroenterological Association Technical Review on the management of hepatitis C. Gastroenterology 2006;130:231-64.
9. Lee SS, Abdo AA. Predicting antiviral treatment response in chronic hepatitis C: How accurate and how soon?. J Antimicrob Chemother 2003;51:487-91.
10. Poordad F, Reddy KR, Martin P. Rapid virologic response: A new milestone in the management of chronic hepatitis C. Clin Infect Dis 2008;46:78-84.
11. Kamal SM, Nasser IA. Hepatitis C genotype 4: What we know and what we don't yet know. Hepatology 2008;47:1371-83.
12. Al-Faleh FZ, Hadad Q, Khuroo MS, Aljumah A, Algamedi A, Alashgar H, *et al*. Peginterferon α-2b plus ribavirin compared with interferon α-2b plus ribavirin for initial treatment of chronic hepatitis C in Saudi patients commonly infected with genotype 4. Liver Int 2004;24:568-74.
13. Kamal SM, El Kamary SS, Shardell MD, Hashem M, Ahmed IN, Muhammadi M, *et al*. Pegylated interferon alpha-2b plus ribavirin in patients with genotype 4 chronic hepatitis C: The role of rapid and early virologic response. Hepatolgy 2007;46:1732-40.
14. Gad RR, Males S, El Makhzangy H, Shouman S, Hasan A, Attala M, *et al*. Predictors of a sustained virological response in patients with genotype 4 chronic hepatitis C. Liver Int 2008;28:1112-9.
15. Itraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. Hepatology 1994;20:15-20.
16. Hasan F, Asker H, Al-Khaldi J, Siddique I, Al-Ajmi M, Owaid S, *et al*. Peginterferon Alfa-2b plus ribavirin for the treatment of chronic hepatitis C genotype 4. Am J Gastroenterol 2004;99:1733-7.
17. Al Ashgar H, Helmy H, Khan MQ, Al Kahtani K, Al Quaiz M, Rezeig M, *et al*. Predictors of sustained virological response to a 48-week course of pegylated interferon alfa-2a and ribavirin in patients infected with hepatitis C virus genotype 4. Ann Saudi Med 2009;29:4-14.
18. Poynard T, McHutchison J, Goodman Z, Ling MH, Albrecht J. Is an "a la carte" combination interferon alfa-2b plus ribavirin regimen possible for the first line treatment in patients with chronic hepatitis C? The ALGOVIRC Project Group. Hepatology 2000;31:211-8.
19. Zeuzem S, Hulcrantz R, Bourliere M, Goeser T, Marcellin P, Sanchez-Tapias J, *et al*. Peginteferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3. J Hepatol 2004;40:993-9.
20. Hourigan LF, Macdonald GA, Purdie D, Whitehall VH, Shorthouse C, Clouston A, *et al*. Fibrosis in chronic hepatitis C correlates significantly with body mass index and steatosis. Hepatology 1999;29:1215-9.
21. Clouston AD, Jonsson JR, Purdie DM, Macdonald GA, Pandeya N, Shorthouse C, *et al*. Steatosis and chronic hepatitis C: Analysis of fibrosis and stellate cell activation. J Hepatol 2001;34:314-20.
22. Adinolfi LE, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. Hepatology 2001;33:1358-64.
23. Backus LI, Boothroyd DB, Phillips BR, Mole LA. Predictors of response of US veterans to treatment for the hepatitis C virus. Hepatology 2007;46:37-47.
24. Ge D, Fellay J, Thompson AJ, Thompson AJ, Simon JS, Shianna KV, *et al*. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature 2009;461:399-401.
25. Mangia A, Thompson AJ, Santoro R, Piazzolla V, Tillmann HL, Patel K, *et al*. An IL28B polymorphism determines treatment response of hepatitis C virus genotype 2 or 3 patients who do not achieve a rapid virological response. Gastroenterology 2010;139:821-7.
26. Asselah T, De Muynck S, Broët P, Masliah-Planchon J, Blanluet M, Bièche, *et al*. IL28B polymorphism is associated with treatment response in patients with genotype 4 chronic hepatitis C. J Hepatol 2012;56:527-32.
27. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, *et al*. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011;364:2405-16.
28. Poordad F, McCone J Jr, Bacon BR, Bruno S, Manns MP, Sulkowski MS, *et al*. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1195-206.

How to cite this article: Ismail MH. Prediction of sustained virologic responses to combination therapy of pegylated interferon-α and ribavirin in patients with chronic hepatitis C infection. J Fam Community Med 2013;20:35-40.
Source of Support: Nil, **Conflict of Interest:** Nil