Sustained Virological Response Rates to Antiviral Therapy in Genotype 1 and 3 Chronic Hepatitis C Patients: A Study from North India

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Background: In India, both genotype 3 and 1 are predominant genotypes in patients with chronic hepatitis C (CHC). However, there is scanty data on sustained viral response (SVR) rate with conventionally recommended dual therapy with PEG-IFN and ribavirin. **Methods:** In this retrospective study, consecutive patients of CHC of genotypes 1 and 3, attending the single unit of Gastroenterology of our hospital, who received PEG-IFN and ribavirin therapy, were included. Patients who had co-infection with HIV or HBV were excluded. **Results:** A total of 114 patients were included in the study median age 44 (15–72) years, 79% males. Most common presentation was with chronic hepatitis, while 10 (9%) patients had compensated cirrhosis. Nine (8%) patients had associated diabetes, 16 (14%) patients gave history of significant alcohol abuse. The median baseline HCV RNA level was 3.0×10^5 (1.7×10^3 – 1.8×10^7) IU/mL. The most common genotype was 3 (75%) followed by genotype 1 (25%). 70% patients received PegIFN- α 2a (median dose 180 MIU/wk) and 30% patients received PegIFN- α 2b (median dose 80 MIU/wk). The median ribavirin dose was 800 (range 800–1200) mg. SVR in genotype 1 was 64% (18/28) while SVR in genotype 3 was 73% (63/86). The factors predicting SVR on univariate analysis were a lower baseline HCV RNA level (less than 3.0×10^5), higher hemoglobin level > 11.8 g/dl, and achievement of rapid virological response (RVR), early virological response (EVR) and end of treatment response (ETR). In multivariate analysis the only baseline factor found independently correlating with SVR was low HCV RNA level ($< 3.0 \times 10^5$ IU/mL) ($P = 0.003$). **Conclusion:** In north India, HCV genotype 3 has a SVR rate of 73%, which is comparable to genotype 1 with SVR rate of 64% when treated with PEG-IFN and ribavirin therapy. A baseline HCV RNA level lower than 3.0×10^5 best predicts SVR in addition to achievement of RVR, EVR or ETR. (J CLIN EXP HEPATOL 2014;4:287–292)

Hepatitis C virus (HCV) is an important cause of liver disease and one of the most important treatable cause of liver disease worldwide. Even though, the structure of Hepatitis C virus has been completely outlined in recent years, an effective and safe therapy of hepatitis C remains problematic in a large majority of patients.¹ Genotype is one of the strongest prognostic aspects of sustained virological response.² The prevalence of infection with various genotypes varies in different countries and regions within the same country.^{3,4}

Different ethnic groups respond differently to standard therapy of HCV and hence there is variation in SVR rates.⁵

About 50% of HCV patients do not attain sustained virological response with the availability of current dual therapy of PEG-IFN and ribavirin.⁶ In recent years direct acting antiviral (DAA) agents have emerged in the horizon of anti HCV therapy.⁷ A substantial amount of time will take before these drugs get available in Indian market at an affordable price. Indians have to still rely upon conventional therapy, with PEG-IFN and ribavirin. The purpose of this study was to evaluate the efficacy of PEG-IFN and RBV in Chronic hepatitis C genotype 1 and 3 from India, and document the SVR rates, taking into consideration various predictive factors.

Keywords: hepatitis C virus, liver disease, interferon, antivirals, sustained viral response

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Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CHC: chronic hepatitis C; ETR: end of treatment response; EVR: early virological response; G-CSF: granulocyte colony stimulating factor; HCV: hepatitis C virus; HIV: human immunodeficiency virus; NS: not significant; PCR: polymerase chain reaction; PEG-IFN: pegylated interferon; RVR: rapid virological response; SVR: sustained virological response; TLC: total leukocyte count

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PATIENTS AND METHODS

Patients

In this retrospective study, consecutive patients of age 15–75 years with CHC genotype 1 and 3 who were treatment naïve, and were eligible for antiviral therapy were enrolled for study. Patients who received even a single dose of PEG-IFN were included in the study and were analyzed as per intention-to-treat analysis. Patients were excluded if they

were positive for IgM antibody to hepatitis A virus or hepatitis E virus, hepatitis B surface antigen, antibody to HIV, autoimmune disease, end-stage renal disease, significant psychiatric disease that precludes therapy with interferon, and symptomatic cardiovascular diseases. Further, patients with mixed genotype were excluded.

Definitions

Patients Eligible for Antiviral Therapy

All patients with CHC who were treatment naïve were eligible for therapy. CHC was defined by the presence of antibodies to HCV by means of third-generation enzyme-linked immunosorbent assay (ELISA), elevated alanine aminotransferase (ALT) levels, and detectable HCV RNA by quantitative real-time polymerase chain reaction (PCR) assay (Cobas Taqmen 48). Patients who had advanced liver disease in form of Child's B or C cirrhosis or liver failure were not eligible for therapy. If indicated liver biopsy was done to estimate stage of fibrosis and to rule out cirrhosis. Patients with bridging fibrosis or cirrhosis were not excluded, provided they had compensated liver disease (Child-Pugh class A).

Rapid Virologic Response (RVR)

Defined as undetectable HCV RNA at week 4.

Early Virologic Response (EVR)

Defined as $\geq 2 \log_{10}$ reduction from baseline HCV RNA, but virus remains detectable (partial EVR) or is undetectable (complete EVR) at week 12.

End-of-treatment Response (ETR)

Defined as HCV RNA negative by a sensitive test at the end of 24 or 48 weeks of treatment (as per AASLD criteria). Patients whose ETR results were not available due to lost to follow up were considered as failed to have achieved ETR (intention-to-treat analysis).

Sustained Virological Response (SVR)

Defined as undetectable HCV RNA at 24 weeks after treatment completion. Patients whose SVR results were not available due to lost to follow up were considered as failed to have achieved SVR (intention-to-treat analysis).

Baseline Evaluation

Each patient underwent clinical evaluation in terms of history, physical examination and laboratory and radiological evaluation. Patients with significant alcohol intake were defined as those who were consuming regularly >20 g of alcohol per day prior to therapy for at least ten years. Complete blood count, liver function test, renal function test, prothrombin time, INR, ultrasound abdomen, Hepatitis B surface antigen, HIV, ANA, ASMA, baseline HCV RNA by quantitative real-time polymerase chain reaction (PCR)

assay (Cobas Taqmen 48), HCV genotype by real-time polymerase chain reaction (PCR) assay were done for all patients. 25(OH) Vitamin D3 level was done in some of the patient. The diagnosis of cirrhosis was based on clinical, biochemical, and imaging (Ultrasound, computed tomography/magnetic resonance imaging [CT/MRI]) parameters. Liver biopsy was done if clinically indicated.

Antiviral Therapy

All eligible patients were started on a combination therapy of PEG-IFN ($\alpha 2a$ or $\alpha 2b$) subcutaneously plus oral ribavirin (RBV) at dosages recommended in the treatment guidelines. Peg-IFN $\alpha 2a$ was given at a dose of 180 mcg subcutaneously per week and Peg-IFN $\alpha 2b$ was given at a dose of 1.5 mcg/kg subcutaneously per week. Ribavirin was given at a dose of 800 mg/day for genotype 3 patients and at a dose of 1000 mg for those <75 kg in weight and 1200 mg for those >75 kg in genotype 1 patients.

On Therapy Monitoring

Physical signs, adverse effects, drug compliance, complete blood counts, and serum aminotransferases were monitored every week for first month followed by once in a month till the end of therapy. Drug dose was modified in patients developing clinically significant adverse events.

Follow-up

HCV RNA assays were done at baseline, at 4-week (RVR), at 12-week (EVR), at end of therapy (ETR) and at 6 months after the completion of therapy (SVR). The primary efficacy parameter in this study was SVR. Patients with positive HCV RNA at the end of therapy (virological breakthrough), as well as those with virological relapse, were classified as non-responders. Age, gender, associated diabetes, BMI, alcohol abuse, hemoglobin, serum ALT and AST, HCV genotype, baseline viral load and ETR were analyzed for predictors of SVR.

Statistical Analysis

Continuous data was represented as median (range) and compared using Mann-Whitney U test. Categorical data was expressed as number and percentage and compared using Fisher's exact test or Chi square test. Factors found significantly predicting SVR on univariate analysis were entered into multivariate analysis by binary logistic regression to determine independent factors predicting response. Statistical analysis was done using SPSS 17.0 (Chicago, Illinois).

RESULTS

Patients

A total of 127 patients, who presented to our hospital between 2009 and 2013, were enrolled for the study as per

the inclusion criteria. Thirteen patients were excluded due to following reasons: concomitant hepatitis B surface antigen ($n = 3$), presence of antibody to HIV ($n = 2$), autoimmune disease ($n = 2$), ESRD ($n=3$), symptomatic cardiac or cardiovascular diseases ($n = 1$), with mixed genotype ($n = 2$). The remaining 114 patients were included in the study.

Baseline Characteristics

The baseline characteristics of included 114 patients are shown in Table 1. The median age of patients was 44 (15–72) years and majority (79%) were males. Presentation was with chronic hepatitis in majority of patients (104/114, 91%); while only 10 (9%) patients had compensated cirrhosis. Among the risk factors for HCV acquisition, 19 (17%) patients had a history of blood transfusion, 28 (25%) had history of surgery, 2 (2%) were intravenous drug users, 4 (4%) had dental extraction and the remaining 61 (53%) patients had no known risk factors. Sixteen (14%) patients gave history of significant alcohol abuse and 9 (8%) patients had associated diabetes. The median baseline HCV RNA level was 3.0×10^5 (1.7×10^3 – 1.8×10^7) IU/mL. The most common genotype was 3 (86, 75%) followed by 1

(28, 25%). The baseline biochemical parameters and HCV RNA levels were similar in both the genotypes.

Treatment Received and Side-effects

Seventy percent patients received PEG-IFN- α 2a (median dose 180 MIU/wk) with ribavirin and 30% patients received PEG-IFN- α 2b (median dose 80 MIU/wk) with RBV. The median RBV dose was 800 (range 800–1200) mg.

Therapy with PEG-IFN and RBV was well tolerated and only a few adverse events were encountered. Fever was encountered in 26 (23%), anemia in 20 (18%), thrombocytopenia in 17 (15%) and neutropenia in 25 (22%). Five (4%) patients were given G-CSF while none of the patient received erythropoietin. Psychiatric symptoms and insomnia were not reported by any of the patients. There was no significant difference observed in frequency and nature of side effects between patients of genotype-1 and 3 with therapy with PEG-IFN and RBV.

Treatment Response

Rapid Virological Response (RVR)

Of the 114 patients, RVR could be tested in 112 patients. RVR was achieved in 56/112 (50%) patients. RVR in

Table 1 Clinical Characteristics of Patients and Factors Associated with SVR.

Parameters	All patients ($n = 114$)	Patients with SVR ($n = 81$)	Patients without SVR ($n = 33$)	P value
Age	44 (15–72)	44 (15–70)	44 (21–65)	0.781
Gender				0.205
Male	90 (79%)	61 (75%)	29 (88%)	
Female	24 (21%)	20 (25%)	4 (12%)	
Presentation				0.277
Chronic hepatitis	104 (91%)	72 (89%)	32 (97%)	
Cirrhosis	10 (9%)	9 (11%)	1 (3%)	
Diabetes	9 (8%)	7 (9%)	2 (6%)	1.000
Significant alcohol use	16 (14%)	11 (14%)	5 (15%)	0.776
Risk factors				
Blood transfusion	19 (17%)			
Surgery	28 (25%)			
Needle stick injury	0 (0%)			
Tattoo	0 (0%)			
Dental extraction	4 (4%)			
IV drug abuse	2 (2%)			
Multiple sexual partners	1 (1%)			
BMI	25.1 (16.3–35.8)	25.2 (16.3–35.8)	24.9 (20.8–34.7)	0.680
Hemoglobin	13.0 (9.0–17.3)	13.2 (9.3–17.0)	12.0 (9.0–17.3)	0.008
TLC ($\times 10^3$/cumm)	5.8 (2–10.7)	6.0 (2.0–10.7)	5.0 (2.3–10.0)	0.132
Platelets ($\times 10^3$/cumm)	180 (35–390)	180 (46–370)	164 (35–390)	0.685
Bilirubin	1 (0.3–5.2)	1.0 (0.3–5.2)	1.1 (0.5–3.6)	0.275

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Table 1 (Continued)

Parameters	All patients (n = 114)	Patients with SVR (n = 81)	Patients without SVR (n = 33)	P value
AST	71 (26–447)	74 (28–447)	67 (26–169)	0.891
ALT	64 (13–541)	64 (13–541)	66 (18–232)	0.970
Albumin	3.9 (2.2–5.2)	3.9 (2.4–5.2)	3.8 (2.2–5.0)	0.234
Creatinine	0.9 (0.4–1.4)	0.9 (0.4–1.4)	1.0 (0.4–1.3)	0.335
Baseline HCV RNA	3.0×10^5 (1.7×10^3 – 1.8×10^7)	2.2×10^5 (1.7×10^3 – 1.6×10^7)	6.4×10^5 (2.5×10^4 – 1.8×10^7)	0.043
HCV Genotype				0.472
Genotype 1	28 (25%)	18 (22%)	10 (30%)	
Genotype 3	86 (75%)	63 (78%)	23 (70%)	
Type of PEG-IFN				0.112
$\alpha 2a$	78 (68%)	59 (73%)	19 (58%)	
$\alpha 2b$	36 (32%)	22 (27%)	14 (42%)	
RVR				<0.0001
Achieved	56/112 (50%)	50/80 (62%)	6/32 (19%)	
Not achieved	56/112 (50%)	30/80 (38%)	26/32 (81%)	
EVR				<0.0001
Achieved	77 (68%)	69 (85%)	8 (24%)	
Partial EVR	16 (14%)	10 (12%)	6 (18%)	
Not achieved	21 (18%)	2 (3%)	19 (58%)	
ETR				<0.0001
Achieved	89 (78%)	81 (100%)	8 (24%)	
Not achieved	25 (22%)	0 (0%)	25 (76%)	

Abbreviations: SVR, sustained virological response; BMI, body mass index; TLC, total leukocyte count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HCV, hepatitis C virus; RNA, ribonucleic acid; PEG-IFN, pegylated interferon; RVR, rapid virological response; EVR, early virological response; ETR, end of treatment response.

genotype 1 was 41% (11/27) while RVR in genotype 3 was 53% (45/85).

Early Virological Response (EVR)

Complete EVR was achieved in 77 (68%) patients while 16 (14%) patients achieved partial EVR. In genotype 1, 14/28 (50%) patients achieved complete EVR and 7/28 (25%) patients achieved partial EVR. In genotype 3, 63/86 (73%) patients achieved complete EVR and 9/86 (10%) patients achieved partial EVR.

End-of-treatment Response (ETR)

It was achieved in 89/114 (78%) patients. ETR in genotype 1 was 68% (19/28) while ETR in genotype 3 was 81% (70/86).

Sustained Virological Response (SVR)

It was achieved in 81/114 (71%) patients. SVR in genotype 1 was 64% (18/28) while SVR in genotype 3 was 73% (63/86).

Factors Associated with SVR

Table 1 shows factors found to be associated with SVR. The factors associated with SVR in univariate analysis were a lower baseline HCV RNA level, higher hemoglobin level along with achievement of RVR, EVR and ETR.

Cirrhosis, diabetes, and significant alcohol abuse had no effect on SVR, which might be due to the smaller number of patients in these groups. Even genotype 1 and 3 had similar SVR rates (64% and 73% respectively, $P = \text{NS}$).

Following factors were included in the multivariate analysis: HCV RNA level and hemoglobin (based on univariate analysis), EVR (most clinically useful parameter) and cirrhosis and genotype (based on existing knowledge). The only factors found independently correlating with SVR were lower HCV RNA level and achievement of EVR (Table 2).

Baseline HCV RNA level of 3.0×10^5 IU/mL was found to be the best cut-off that can predict SVR, as obtained by receiver operating curve and Youden's index. Of 57

patients who had HCV RNA level below this cut off, 48 (84%) achieved SVR; while of remaining 57 patients baseline HCV RNA level was higher than this cut off, only 33 (58%) could achieve SVR ($P = 0.003$).

DISCUSSION

Only 20 years after the discovery of the hepatitis C virus (HCV), a cure is now likely for most people affected by this chronic infection, which carries a substantial disease burden worldwide. Many additional potent agents are in the clinical pipeline, and interferon-free regimens are likely to dominate the HCV therapeutic landscape.⁸ In India we still have to wait for a long time before these newer drugs are freely available. As of now PEG-IFN and ribavirin is still the therapy of choice for HCV patients in our population besides having many side effects.⁹ We evaluated the efficacy of PEG-IFN and RBV in northern Indian population suffering from chronic hepatitis C genotype 1 and 3 infection and documented the SVR rates, taking into consideration various predictive factors.

The response of patients with CHC to PEG-IFN plus RBV therapy is heterogeneous.¹⁰ Previous studies done from different geographical and ethnic areas indicate that among patients infected with HCV genotype 3, SVR was achieved in 68–83% patients.^{11,12} In CHC genotype 1 patients a SVR rate of 42–56% was achieved.^{11,13} Studies carried out in the Indian subcontinent population have shown poor response to therapy.^{14,15} In a study by freshwater et al in genotype 3 CHC patients, Asian population achieved 42.1% SVR in comparison to Caucasians population which achieved SVR of 62.1%. There is limited data on genotype 1 response rate from India. In our study we compared SVR rates in CHC genotype 1 and 3 in north Indian population. 64% of patients achieved SVR in genotype 1 and 73% patients achieved SVR in genotype 3. There was no statistical significant difference in SVR rates of genotypes 1 and 3. SVR achieved in our study population was higher in comparison to available Indian data. This indicates that patient characteristics, and ethnicity could be a possible

explanation for different SVR rates in different study population. Probably due to the small CHC genotype 1 population in our study, SVR achieved in CHC genotype 1 and 3 were comparable. Another hypothesis could be that CHC genotype 1 may be a milder form in Indian population. In a study by Chen-Hua Liu in Hepatitis C patients with genotype 1 in Asian population, patients who received 48 weeks of therapy had a significantly higher SVR rate of 76%.¹⁶ Further studies with large study population are needed to confirm these findings in Indian population.

Predictors of a sustained virological response have been defined previously. A baseline viral load below 400,000–800,000 IU/ml, Asian and Caucasian ethnicity, younger age, low GGT levels, absence of advanced fibrosis/cirrhosis, and absence of steatosis in the liver can predict good response with PEG-IFN and ribavirin therapy in patients with chronic hepatitis C genotypes 3 infection.¹⁷ A study by Tohra et al from India concluded that Age, BMI, and alcohol consumption play an important role in determining treatment outcome in genotype 3 CHC infection.¹⁸ There is no Indian data predicting treatment response in genotype 1 CHC infection. In our study the factors predicting SVR in univariate analysis were a lower baseline HCV RNA level, higher hemoglobin level and achievement of RVR, EVR and ETR. Higher hemoglobin may prevent side effects with PEG-IFN and ribavirin therapy and thus ensuring better tolerability and compliance with antiviral therapy. In multivariate analysis the only baseline factor found independently correlating with SVR was lower HCV RNA level. RVR, EVR and ETR are important treatment related factors predicting SVR ($P < 0.001$). In a study by Chen-Hua Liu in Hepatitis C patients with genotype 1, a baseline serum HCV RNA level $< 8 \times 10^5$ IU/mL was a good predictor of treatment response.¹⁶ Using receiver operating curve on HCV RNA value a cut off of 3.0×10^5 IU/mL achieved SVR in 84% of patients, including both genotype 1 and 3 ($P = 0.003$). Thus a lower HCV RNA at the start of therapy predicts a better outcome.

In our study factors like age, gender, BMI, ALT level, cirrhosis, associated diabetes and alcohol abuse were not significantly associated with SVR. Although the absence of cirrhosis is one of the factors associated with an increased chance of SVR, it is not known to what extent and in what manner the baseline liver fibrosis score impacts on the SVR rate.¹⁹ In our study population side effects with PEG-IFN and ribavirin therapy were comparable in both genotype 1 and 3 infection. 15–20% of our patients reported one or the other side effect of antiviral therapy.^{20,21}

In recent years direct acting antiviral (DAA) agents have emerged in the horizon of anti HCV therapy and some of them like sofosbuvir may have an efficacy of achieving 100% SVR.⁷ However these DAA's agents are only available in some of the western countries and that too at an

Table 2 Multivariate Analysis of Factors Predicting SVR.

Parameter	P value	Odds ratio	95% Confidence interval
High hemoglobin level (>11.8 g/dL)	0.440	–	–
Low baseline HCV RNA level ($< 3.0 \times 10^5$ IU/mL)	<0.0001	10.0	2.8–36.3
Cirrhosis	0.966	–	–
Genotype	0.482	–	–
EVR achieved	<0.0001	29.4	7.0–125

Abbreviations: HCV, hepatitis C virus; RNA, ribonucleic acid; EVR, early virological response.

enormously high price. India being an economical weaker country and with high burden of HCV disease, we Indian have to still rely upon conventional therapy, with PEG-IFN and ribavirin, which has stood the test of time. In this respect our study adds significant information to the data on response to HCV therapy in India.

In conclusion, in north India genotype 1 may be a milder form of disease, hence the SVR rates achieved were comparable to those of genotype 3. However a larger study would be needed to confirm these findings. In addition we found that a baseline HCV RNA level lower than 3.0×10^5 best predicts SVR both in genotype 1 and genotype 3 patients. Hence till the availability of direct acting antiviral (DAA) drugs, PEG-IFN and ribavirin may be curative in at least 2/3rd patients and will continue to be the mainstream anti HCV therapy at least in near future.

CONFLICTS OF INTEREST

All authors have none to declare.

REFERENCES

1. Jawaid A, Khuwaja AK. Treatment and vaccination for hepatitis C: present and future. *J Ayub Med Coll Abbottabad JAMC*. 2008 Mar;20(1):129–133.
2. Zein NN, Rakela J, Krawitt EL, Reddy KR, Tominaga T, Persing DH. Hepatitis C virus genotypes in the United States: epidemiology, pathogenicity, and response to interferon therapy. Collaborative Study Group. *Ann Intern Med*. 1996 Oct 15;125(8):634–639.
3. Foster GR. Pegylated interferon with ribavirin therapy for chronic infection with the hepatitis C virus. *Expert Opin Pharmacother*. 2003 May;4(5):685–691.
4. Ghany MG, Strader DB, Thomas DL, Seeff LB, American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatol Baltim Md*. 2009 Apr;49(4):1335–1374.
5. Idrees M, Riazuddin S. A study of best positive predictors for sustained virologic response to interferon alpha plus ribavirin therapy in naive chronic hepatitis C patients. *BMC Gastroenterol*. 2009;9:5.
6. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet*. 2001 Sep 22;358(9286):958–965.
7. Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med*. 2013 Jan 3;368(1):34–44.
8. Liang TJ, Ghany MG. Current and future therapies for hepatitis C virus infection. *N Engl J Med*. 2013 May 16;368(20):1907–1917.
9. Baldick CJ, Wichroski MJ, Pendri A, et al. A novel small molecule inhibitor of hepatitis C virus entry. *PLoS Pathog*. 2010;6(9):e1001086.
10. Zeuzem S. Heterogeneous virologic response rates to interferon-based therapy in patients with chronic hepatitis C: who responds less well? *Ann Intern Med*. 2004 Mar 2;140(5):370–381.
11. Garg G, Kar P. Management of HCV infection: current issues and future options. *Trop Gastroenterol Off J Dig Dis Found*. 2009 Mar;30(1):11–18.
12. Slavenburg S, Weggelaar I, van Oijen MGH, Drenth JPH. Optimal length of antiviral therapy in patients with hepatitis C virus genotypes 2 and 3: a meta-analysis. *Antivir Ther*. 2009;14(8):1139–1148.
13. Kogure T, Ueno Y, Fukushima K, et al. Pegylated interferon plus ribavirin for genotype 1b chronic hepatitis C in Japan. *World J Gastroenterol WJG*. 2008 Dec 21;14(47):7225–7230.
14. Freshwater DA, O'Donnell K, Mutimer DJ. Inferior response of Asian vs non-Asian hepatitis C genotype 3 infection to combination antiviral therapy. *J Viral Hepat*. 2008 Feb;15(2):115–119.
15. Sood A, Midha V, Sood N, Bansal M. Pegylated interferon alfa 2b and oral ribavirin in patients with HCV-related cirrhosis. *Indian J Gastroenterol Off J Indian Soc Gastroenterol*. 2006 Dec;25(6):283–285.
16. Liu C-H, Liu C-J, Lin C-L, et al. Pegylated interferon-alpha-2a plus ribavirin for treatment-naive Asian patients with hepatitis C virus genotype 1 infection: a multicenter, randomized controlled trial. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2008 Nov 15;47(10):1260–1269.
17. Kau A, Vermehren J, Sarrazin C. Treatment predictors of a sustained virologic response in hepatitis B and C. *J Hepatol*. 2008 Oct;49(4):634–651.
18. Tohra SK, Taneja S, Ghosh S, et al. Prediction of sustained virologic response to combination therapy with pegylated interferon alfa and ribavirin in patients with genotype 3 chronic hepatitis C. *Dig Dis Sci*. 2011 Aug;56(8):2449–2455.
19. Shiffman ML, Di Bisceglie AM, Lindsay KL, et al. Peginterferon alfa-2a and ribavirin in patients with chronic hepatitis C who have failed prior treatment. *Gastroenterology*. 2004 Apr;126(4):1015–1023 [discussion 947].
20. Hadziyannis SJ, Sette H, Morgan TR, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med*. 2004 Mar 2;140(5):346–355.
21. Lindahl K, Stahle L, Bruchfeld A, Schvarcz R. High-dose ribavirin in combination with standard dose peginterferon for treatment of patients with chronic hepatitis C. *Hepatol Baltim Md*. 2005 Feb;41(2):275–279.