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Demographic profile, host, disease & viral predictive factors of response in patients with chronic hepatitis C virus infection at a tertiary care hospital in north India

Sreejith Vasudevan, Shalimar, Amit Kavimandan, Nancy Kalra, Baibaswata Nayak, Bhaskar Thakur*, Prasenjit Das**, Siddhartha Datta Gupta**, Subrat Kumar Panda** & Subrat Kumar Acharya

*Departments of Gastroenterology, *Biostatistics & **Pathology, All India Institute of Medical Sciences, New Delhi, India*

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***Background & objectives*: Standard of care for chronic hepatitis C (CHC) in India is peginterferon and ribavirin (RBV). The response to treatment in real life stetting is unclear. The objectives of this study were to evaluate the demographic profile and assess the virological response and predictors of response in CHC patients.**

***Methods*: Consecutive patients with CHC were included in this study. Detailed clinical history, risk factors, and predictive factors of response were noted. Patients were treated with peginterferon α2b (1.5 µg/kg/wk) and RBV (12 mg/kg/day) for 6 to 18 months based on response.**

***Results*: A total of 211 patients were included in the analysis, mean age 40.6±12.3 yr, 144 (68%) were males and 71 (34%) had compensated cirrhosis. Commonest risk factor for acquiring CHC was previous transfusion and surgery (51%). Genotype 3 (72%) was most common followed by genotype 1 (23%). Overall sustained virologic response (SVR) was 64 per cent [95% CI 57.1%-70.4%]. The SVR was 66.5 per cent [95% CI 58.34-73.89%] for genotype 3 and 61.2 per cent [95% CI 46.23 to 74.80%] for genotype 1. Non-cirrhotics had better SVR rates compared to cirrhotics (76 vs 41%, *P*<0.001). On multivariate analysis, BMI ≥23 kg/m², HOMA-IR ≥2, compliance (≤80%), and fibrosis >2 were predictors of low SVR.**

***Interpretation & conclusions:* Genotype 3 was the commonest HCV genotype. The commonest source of infection was previous transfusion and surgery. SVR rates for genotypes 3 were better than genotype 1 patients. Predictors of non-response were high BMI, insulin resistance, significant fibrosis and inadequate compliance.**

Key words Erythropoietin - fibrosis - genotype - peginterferon - ribavirin - sofosbuvir

Hepatitis C virus (HCV) is implicated in 15-20 per cent cases of cirrhosis and hepatocellular carcinoma (HCC) in India[1]. The treatment of HCV infection has improved rapidly, and with the introduction of directly acting antiviral (DAAs) agents, cure in chronic HCV infection is possible now in more than 90 per cent of the patients[2]. However, in India such therapies are presently not available and are likely to be very expensive. In the absence of State funding or insurance reimbursement, most patients in India bear the cost of therapy themselves. Further, unlike in the western world and Japan where genotype 1 HCV is prevalent, genotype 3 HCV is prevalent in India[1]. Peginterferon with ribavirin (RBV) in weight based doses is currently the standard of care for chronic HCV infection in India. The Indian National Association for the Study of Liver (INASL) has also recommended peginterferon α (2a or 2b) and weight based RBV (15 mg/kg/day) in all genotypes as first line therapy[3]. DAAs are not available in many other countries in South Asia, South East Asia and Africa.

Various factors related to the host, disease and virus have been reported to play a role in the outcome of treatment with peginterferon and RBV in CHC. Host predictive factors include age[4], gender[4], obesity and insulin resistance[5], significant alcohol consumption[6], compliance to drugs and biochemical parameters like serum cholesterol[7], ferritin[8], vitamin D3 levels[9], and interleukin (IL)-28B polymorphism[10]. The disease predictive factors include advanced liver disease (imaging or histological evidence of high degree of fibrosis and necroinflammation)[11]. The viral predictive factors include genotype[4], baseline viral load[4] and viral kinetics[12]. The results of various studies are not consistent highlighting the variable effects of these factors in predicting response.

There are extensive data regarding the demographic profile, sustained virologic response (SVR) and predictors of response in CHC treatment available from the West, where genotype 1 is predominant. However, information regarding the SVR and the real life predictors of response in a genotype 3 predominant population is scarce in literature. The present study was undertaken with the objective to evaluate the demographic profile, virological response and assessment of the predictors of response in consecutive, eligible for treatment hepatitis C patients at a tertiary care hospital in India.

Material & Methods

The study was conducted in the department of Gastroenterology, All India Institute of Medical Sciences (AIIMS), New Delhi, India. Patients treated from 2002 to 2010 were included retrospectively and those treated from 2011 to 2013 were included prospectively. Written consent was taken from all patients. The study protocol was cleared by the Institute Ethics Committee.

Diagnosis of CHC: The diagnosis of CHC was made in patients with detectable HCV RNA, with raised alanine aminotransferase (ALT) either intermittently or persistently over a six month period and liver biopsy documenting presence of necroinflammatory activity and/or periportal fibrosis suggestive of chronic hepatitis[13].

Inclusion criteria: All patients with Child A Status[13] with chronic hepatitis or cirrhosis due to HCV, satisfying either of the following criteria were included in the study: *(i)* persistent ALT elevation of ≥ 2 times the upper limit of normal (ULN) over a six month period; *(ii)* liver biopsy showing a METAVIR F score of ≥ 2[13].

Exclusion criteria: The patients having decompensated cirrhosis, co-morbid conditions such as coronary artery disease, chronic renal failure, chronic obstructive airway disease which are contraindications for peginterferon and RBV, co-infection with HIV and hepatitis B virus infection, pregnancy and lactation, active tuberculosis, malignancy and psychiatric disease, autoimmune disease, Wilson's disease, hepatocellular carcinoma, previous interferon therapy, and those not willing for consent were excluded from the study.

Patient evaluation: All patients underwent a detailed assessment of risk factors for acquiring infection like previous blood transfusion, surgery, needle prick, dental procedures, and intravenous drug use. A detailed history regarding the amount of alcohol intake and presence of diabetes was also noted. Clinical evaluation included anthropometric measurements like body mass index (BMI), waist to hip ratio (WHR). All patients underwent haematological tests (haemoglobin, total leucocyte count, platelet count and international normalized ratio- INR), biochemical tests (serum bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total protein, albumin, urea, creatinine, fasting and postprandial blood glucose), fasting lipid profile, alpha-foetoprotein,

abdominal ultrasonography, upper gastrointestinal endoscopy and triple phase CT of abdomen, as required. In addition, all patients underwent tests for anti-nuclear antibody, anti-smooth muscle antibody, anti-liver kidney microsomal antibodies, 24-h urinary copper, serum copper, serum ceruloplasmin and serum ferritin. Assessment of fasting serum insulin and vitamin D3 levels was done in all patients.

Tests for hepatitis B virus surface antigen (HBs Ag, using commercial ELISA Biorad, Marnes-la-Coguette, France) and HIV positivity (HIV-1 and -2 using ELISA) were also performed. At inclusion, each patient was evaluated for depressive illness and thyroid function test (T3, T4, and TSH). HCV-RNA quantitative estimation was done using a competitive real time PCR (RT-PCR)[14]. HCV viral load was expressed in IU/ml. The HCV genotyping was done by reverse hybridization of 5' UTR with genotype specific probe[15]. All patients underwent a liver biopsy, using an 18-G Menghini's aspiration biopsy needle, after ascertaining that the coagulation profile was normal. The fibrosis in the liver biopsy was staged using the METAVIR scoring system[16]. For female patients, a urine pregnancy test was done prior to starting therapy. All female patients in the reproductive age group were advised to use necessary contraceptive measures and not to conceive at least for a period of one year after the completion of treatment.

Predictors of response: The predictors of response were divided into host, disease and viral predictive factors. Host predictive factors included age, sex, BMI, WHR, homeostatic model assessment estimated insulin resistance (HOMA-IR), presence of diabetes mellitus, serum cholesterol, serum ferritin, serum vitamin D3, alcohol consumption and compliance. To assess these predictive factors, continuous variables were dichotomized by age (≤40, >40 yr), BMI (<23, ≥23 kg/m^2), insulin resistance (HOMA-IR <2, ≥2), cholesterol (< 200, ≥200 mg/dl) and vitamin D3 level (≤50, >50ng/ml).

Disease predictive factors included liver biopsy parameters like histological activity index (HAI), fibrosis, steatosis. The dichotomous values of these predictive factors used were significant fibrosis (F >2), necroinflammatory damage (HAI ≥6) and presence of steatosis (>30% of hepatocyte showing macrovesicular steatosis). The Fibroscan values were categorized as liver stiffness measurement (LSM) >6 Kpa (significant fibrosis)[17].

Viral predictive factors included genotype, baseline viral load and viral kinetics. HCV viral load of >6,00,000 IU/ml was defined as a high viral load. The rapid viral response (RVR) was defined as HCV RNA [target not detected (TND)] at four wk of therapy, early viral response (EVR) was defined as HCV RNA (TND) at 12 wk of therapy, partial EVR (HCV RNA reduction by 2 log at the end of 12 wk of therapy), null response (HCV RNA reduction by less than 2 log at 12 wk of therapy), end of treatment response (ETVR) HCV RNA (TND) at the end of therapy, relapse (HCV RNA detection within 6 months after achieving ETVR), and viral breakthrough (HCV RNA positive after being negative while on treatment)[18]. Types of response were assessed in all patients.

Treatment regimen: All eligible patients were treated with weekly subcutaneous injection of weight based peginterferon α 2b (1.5µg/kg/day) and RBV 12 mg/kg/day in two divided doses. The duration of therapy was as per the response guided therapy (RGT) guidelines[13]. Patients with genotypes 2 and 3 were treated for 24 wk if they had RVR and for 48 wk if they had EVR but no RVR. In patients with partial EVR, the duration of therapy was extended to 72 wk. Patients with genotypes 1 and 4 were treated for 48 wk irrespective of the RVR status. In those with significant fibrosis (>F2) or evidence of cirrhosis on imaging, the treatment duration was extended for another 24 wk. The treatment was stopped at 12 wk in null responders.

Granulocyte macrophage colony-stimulating factor (GM-CSF) was administered (300 µg/wk) when the absolute neutrophil count (ANC) was below 1000/µl and dose was subsequently adjusted to keep the absolute neutrophil count above 1500/µl. Erythropoietin was given at a dose of 10,000 IU/wk if the haemoglobin decreased to below 10 g/dl and its subsequent dose was adjusted to keep the haemoglobin ≥ 10 g/dl[19].

Follow up schedule: All patients who were on treatment were followed up weekly in the liver clinic with a complete blood count, liver and renal function tests till the completion of therapy. During each visit, clinical, psychological, and haematological evaluations were done. The quantitative estimation of HCV RNA was done before starting the therapy, and at 4, 12, 24, 48 and 72 wk of treatment. In addition, viral load estimation was done at six months after completion of treatment (SVR). Adequate compliance was defined as intake of more than 80 per cent of the recommended drugs[20].

Statistical analysis: The normally distributed variables were expressed as mean ± SD, and the continuous variables with skewed distribution were expressed as median (range). Categorical data were presented as proportions. Univariate analysis was performed to assess the factors associated with SVR using an independent t test or Mann-Whitney U test for continuous variables. The chi-square test or Fisher's exact test for categorical variables was used wherever applicable. The continuous variables were dichotomized to assess the effect on SVR. Subsequently, a multivariate logistic regression analysis was performed to identify important variables associated with SVR. Stepwise selection procedure was used in the multivariate analysis. Data were analyzed using SPSS software version 17.0 (SPSS, Chicago, IL) and STATA (version 11).

Results

A total of 1177 patients with evidence of chronic HCV infection were registered in the liver clinic during the study period. The details of the patients included in the current study are highlighted in the Figure. Among

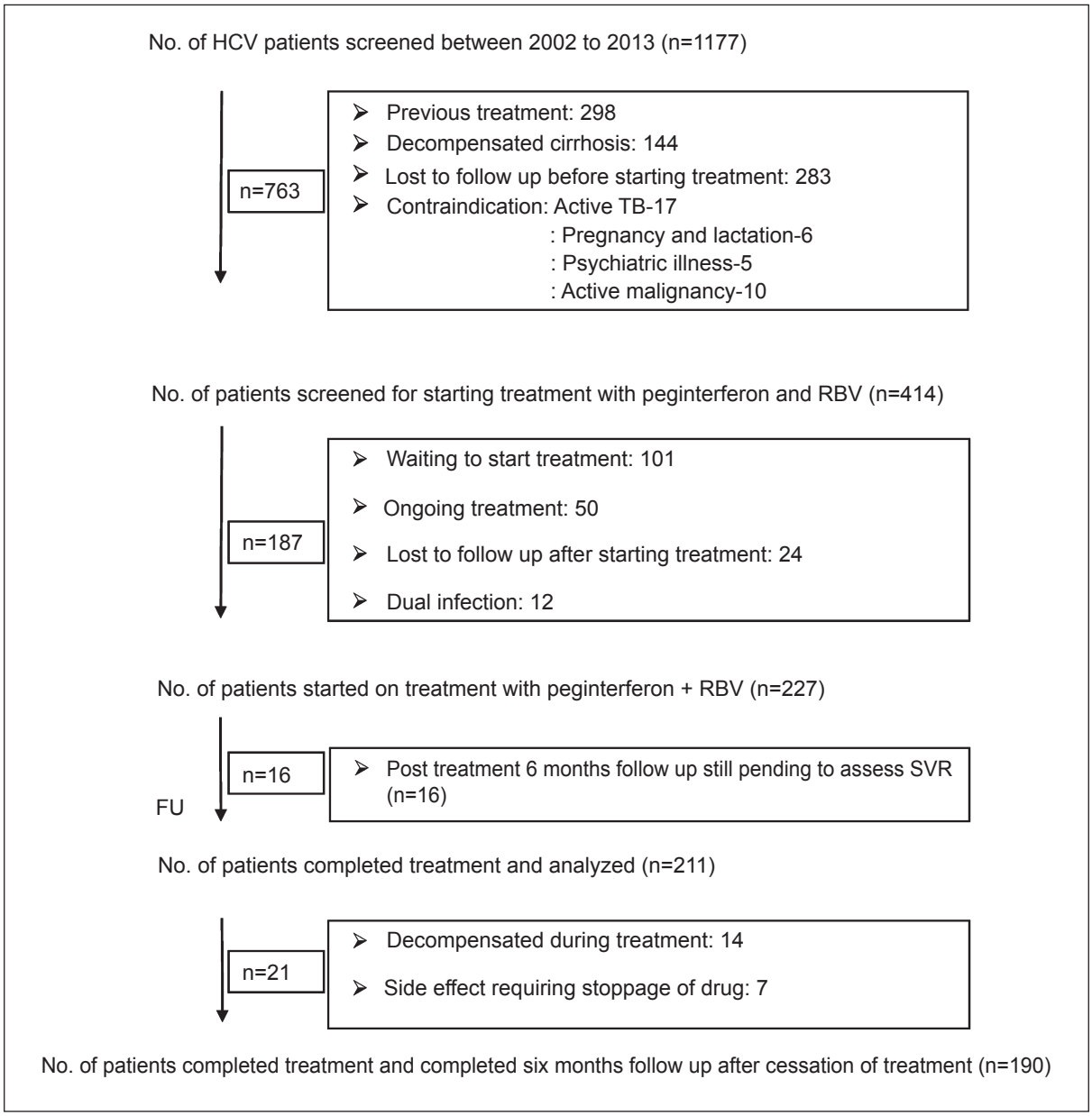

Figure. Details of hepatitis C patients screened and included in the study. SVR, sustained virologic response.

the patients screened, 414 (35.1%) were naïve CHC patients and were eligible for peginterferon and RBV treatment. Two hundred and twenty seven (54.8%) patients completed the scheduled treatment duration. Of these, 211 who completed six months of follow up after cessation of therapy were included for the therapeutic response evaluation. In 21 of these 211, the therapy was discontinued, because of development of decompensation (ascites n=14), or intolerable side effects (n=7).

Demographic profile: The mean age ± SD was 40.6 ± 12.3 yr and 144 (68%) were males. Seventy one (34%) had underlying compensated cirrhosis. A history of alcohol consumption of >20 g/day was present in 26 (12.3%) patients. Twenty four (11.4%) patients had diabetes mellitus. In 108 (51%) patients, transfusion and previous surgery could be implicated as the source of HCV infection. In 46 patients (22%) the source of the infection was uncertain, whereas the probable sources of infection were needlestick injury in 30 (14.2%), dental extraction in 20 (9.4%), haemodialysis in four (1.8%) and intravenous drug abuse in three (1.4%) patients.

Viral and disease characteristics: Genotype 3 was the most common genotype in 152 (72%), followed by genotype 1 in 49 (23%). Genotypes 2, 4 and mixed genotypes were seen in two, six and two patients, respectively (Table I). The median and mean HAI, histological fibrosis score, and median liver stiffness (LSM) as measured by fibroscan in different genotypes are shown in Table II. Baseline median viral load among all the patients was 4.2 X 10^5 (IQR: 6.4 x 10^4- 3.0 x 10^6) IU/ml. Among 152 genotype 3 patients, 88 (58%) had a baseline viral load of more than 600,000 IU/ml, compared with 18 (37%) of 49 genotype 1 patients, (P<0.05). The mean fibrosis score among genotype 3 patients was 2.59 ± 1.83 and among genotype 1 was 2.07 ± 1.38 (P<0.05). The baseline viral load, fibrosis, HAI and LSM were similar between genotypes 3 and 1 patients.

Virological response: The overall SVR rate was 64 per cent (135/211) [95% CI 57.1-70.4]. The SVR rate in genotype 3 patients was 66.5 per cent (101/152) [95 % CI 58.3-73.8] and in genotype 1 was 61.2 per cent (30/49) [95 % CI 46.2-74.8] (Table III). The difference between genotypes 1 and 3 in overall SVR rate was not significant. Twenty one patients (20 genotype 3 and one genotype 1) discontinued treatment due to either decompensation (ascites, n=14) or severe side effects (n=7).

Table I. Baseline demographic, clinical, biochemical, viral and histological characteristics of patients

Variables	(n=211)
Age (yr) Median (range)	40.6 ± 12.3 41 (13-74)
Sex (M:F)	144:67
BMI, kg/m^2 Median (range)	23.1 ± 3.2 22.4 (15.5-36.3)
WHR Median (range)	0.91 ± 0.09 0.89 (0.6-1.19)
Significant alcohol intake n (%)	26 (12%)
Cirrhosis, n (%)	71 (34%)
Diabetes mellitus, n (%)	24 (11%)
ALT, IU/l Median (range)	105.7 ± 83.4 54 (12-358)
HOMA-IR Median (range)	2.4 ± 1.6 2.06 (0.38-8.03)
Ferritin, Median (range), ng/ml	142 (76-240)
Vitamin D3, Median (range), ng/ml	24.5 (15.7-42)
Cholesterol, Median (range), mg/dl	146 (110-260)
Fibroscan, kPa Median (range)	12.54 ± 10.40 8 (3-49)
Fibrosis, kPa Median (range)	2.1 ± 1.5 2 (1-6)
HAI Median (range)	5.6 ± 1.8 2 (2-10)
Genotype distribution, n	
Genotype 1,	49
Genotype 2,	2
Genotype 3,	152
Genotype 4,	6
Mixed genotype	2
Baseline viral load, IU/ml Median (range)	 4.2x10^5 (6.4 x 10^4 - 3.0 x 10^6)

Data are expressed as mean ± SD, n (%) unless otherwise specified
WHR, waist hip ratio; ALT, alanine aminotransferase; HOMA-IR, homeostatic model assessment estimated insulin resistance; HAI, histological activity index

Among the 211 patients, 71 (33.6%) had underlying cirrhosis. Overall, one third of both genotypes 1 and 3 patients had underlying cirrhosis. The SVR in patients with cirrhosis was significantly less as compared with patients without cirrhosis (40.8 vs 75.7%; P = 0.001).

Table II. Viral and histological characteristics among different genotypes

Genotype	3	1	4	2	Mixed genotype
N	152 (72%)	49 (23%)	6 (3%)	2 (1%)	2 (1%)
Median Baseline VL (IU/ml)	$3.4x10^5$ ($269-1.5x10^8$)	$6.7x10^4$ ($801-1.4x10^8$)	$4.4x10^6$ ($11259-1.0x\ 10^8$)	$4.2x10^6$ ($7692-8.4x10^6$)	$1.3x10^7$ ($284000-2.6x10^7$)
Median fibrosis	2 (0-6)	2 (0-6)	1.5 (1-2)	3 (2-4)	1.5 (1-2)
Mean fibrosis	2.59 ± 1.83	2.07 ± 1.38	1.5 ± 0.57	3.0 ± 1.41	1.5 ± 0.70
Median HAI	4 (1-10)	5 (1-9)	3.5 (3-6)	3 (1-6)	4 (0-4)
Median LSM, kPa	8 (3-49)	7.25 (4-35)	5.5 (5-25)	14.5 (5-24)	6.3 (6-8)

All data are expressed as median (range)
VL, viral load; HAI, histological activity index; LSM, liver stiffness measurement

Table III. Sustained virological response (SVR) rates among CHC and cirrhosis patients with different genotypes

Group	Chronic hepatitis			Cirrhosis			All cases		
	Total	SVR		Total	SVR		Total	SVR	
		Number	Per cent		Number	Per cent		Number	Per cent
Genotype 3	100	79	79	52	22	42	152	101	66.5
Genotype 1	32	24	75	17	6	35	49	30	61.2
All genotypes	140	106	75.7	71	29	40.8	211	135	64

The SVR rates among the cirrhotics with genotypes 1 and 3 were 35 per cent (6/17) and 42 per cent (22/52), respectively. There was no significant difference in the SVR between genotypes 3 and 1 among patients with either chronic hepatitis or cirrhosis.

Predictors of response: As our study included both retrospective and prospectively collected data, some of the predictors of response were not available for all patients. Results of univariate analysis of predictive factors with SVR are shown in Table IV.

In the univariate analysis, host factors (age, BMI < 23 kg/m^2, HOMA-IR < 2, compliance of >80%); and disease factors [fibrosis score of ≤2 (≤F2) on histology, fibroscan value of ≤6 kPa, absence of cirrhosis] were independent prognostic indicators of high SVR. The sex distribution, presence of diabetes, significant alcohol consumption, low vitamin D3, high ferritin among the host factors; necroinflammatory activity or steatosis in histology among the disease factors; and baseline viral load among the viral factors were not associated with response. In addition, the three-fourths of the patients who achieved RVR and EVR had SVR.

On multivariate analysis, BMI ≥ 23 kg/m^2, HOMA-IR ≥ 2, compliance of ≤80 per cent (host factors), and significant fibrosis on biopsy (disease factor) were independently predictive of lower SVR (Table V). Among patients with BMI < 23 kg/m^2, 56 (79%) patients had SVR. In patients with BMI (> 23 kg/m^2), 79 (58%) patients had SVR. Similarly, in patients with HOMA-IR (<2.0), 54 (73%) patients had SVR. In patients with fibrosis score of (≤ 2), 85 (75.2%) patients had SVR. In patients with fibrosis score of >2, 29 (46%) patients had SVR. In patients with >80 per cent compliance to drugs, 135 (71%) had SVR whereas, in patients with ≤80 per cent compliance, only two (9.5%) had SVR. The RVR and EVR were significant predictive factors for SVR (Table III).

Safety and side effects: Overall, the combination therapy of peginterferon and RBV was well tolerated in CHC patients. Majority of patients (90%; 190/211) had adequate compliance defined as >80 per cent of intake of drugs. Only 21 (10%) patients could not achieve adequate compliance. Among these 21 patients, 14 (67%) decompensated during treatment and seven (33%) patients discontinued therapy due to side effects which were refractory to supportive measures. The most common side effects were fever in 128 (60.6%), malaise and easy fatigability in 102 (48.3%), headache in 94 (44%), loss of appetite in 68 (32%), insomnia in

Table IV. Univariate analysis of factors associated with sustained virologic response (SVR) (n=211)

	No. of patients	SVR (n=135)		*P* value
		Number	%	
Age (yr): ≤ 40	106	87	82.1	0.001
> 40	105	48	45.7	
Sex: Male	144	90	62.5	0.511
Female	67	45	67.2	
BMI: (kg/m^2) < 23	71	56	78.9	0.002
≥ 23	137	79	57.6	
Waist hip ratio for male: WHR ≤ 0.9	68	39	57.3	0.122
WHR > 0.9	73	51	69.9	
Waist hip ratio for female: WHR ≤ 0.8	6	6	100	0.073
WHR > 0.8	61	39	63.9	
HOMA-IR: < 2	74	54	72.9	0.001
≥ 2	77	36	46.7	
DM: Present	24	12	50.0	0.13
Absent	187	123	65.8	
Vitamin D3 (ng/ml): ≤50	123	72	58.5	0.08
>50	26	20	76.9	
Compliance (%): >80	190	135	71.0	0.001
≤ 80	21	2	9.5	
GCSF: Received	75	40	53.3	0.01
Not received	136	95	69.8	
Erythropoietin: Received	42	14	33.3	0.001
Not received	169	121	71.6	
Fibrosis :≤ 2	113	85	75.2	0.001
> 2	63	29	46.0	
Steatosis : ≤30%: No	94	62	66.0	0.725
>30%: Yes	82	52	63.4	
Fibroscan :≤6 LSM	76	54	71.0	0.005
>6 LSM	78	38	48.7	
Cirrhosis: Absent	140	106	75.7	0.001
Present	71	29	40.8	
Genotype 3	152	101	66.4	0.505
Genotype 1	49	30	61.2	
Baseline VL : ≤ 6,00,000 IU/ml	110	70	63.6	0.913
>6,00,000 IU/ml	101	65	64.3	
RVR: Yes	152	112	73.7	0.001
No	59	23	39.0	
EVR: Yes	170	126	74.1	0.001
No	41	9	21.9	

DM, diabetes mellitus; GCSF, granulocyte colony stimulating factor; LSM, liver stiffness measurement; VL, viral load; RVR, rapid virological response; EVR, early virological response

20 (9.4%) and skin erythema in 12 (6%). These adverse events were mild, self limiting and did not require any dose adjustment or discontinuation of the drugs.

In 130 (62%) patients there was a drop in haemoglobin from the baseline value. One fifth (42) patients had clinically significant haemoglobin drop (< 10 g/dl) requiring erythropoietin therapy. One-third (75) patients had a significant drop in total leucocyte count (< 4000/mm^3, absolute neutrophil count < 750/mm^3). Among the seven patients who discontinued therapy

Table V. Multivariate analysis of various factors predicting sustained virologic response (SVR)

Variables	OR (95% CI)	*P* value
Age (yr) ≥ 40	1	0.490
Age < 40	1.02 (0.96-1.08)	
BMI (kg/m^2) ≥ 23	1	
BMI < 23	16.6 (2.5-100.0)	0.003
HOMA -IR ≥ 2	1	
< 2	20 (4.3-100.0)	0.002
Fibrosis >2	1	
≤ 2	3.8 (1.01-16.6)	0.043
Compliance (%) ≤ 80	1	
> 80	136 (6.7-275.7)	0.001
G-CSF-No	1	
-Yes	2.5 (0.6-11.1)	0.202
Erythropoietin-No	1	
-Yes	1.05 (0.19-5.5)	0.953

due to the side effects, three patients each had severe depression with suicidal intention, severe bicytopenia not responding to growth factors and one had angina.

Discussion

As documented in many earlier studies, the present study also documented that genotype 3 is the most common genotype prevalent in India[21,22]. Further, one third of the patients across genotypes had compensated cirrhosis. This assumes importance, because the median age of patients in the present study was 41 years. HCV is known to cause advanced liver disease over 2 to 3 decades and, unlike HBV, it is acquired later in life[1,3]. The mean fibrosis score was 2.16 ± 1.3 in patients with age < 40 yr (n=106), whereas in patients (> 40 yr) of age (n=105), the score was 2.7 ± 1.5. This cross-sectional data, documenting significant fibrosis at a relatively younger age (< 40 yr), may imply that genotype 3 cases have a more rapid progressive course. This is of concern because genotype 3 is more frequently associated with hepatocellular carcinoma, especially in the presence of cirrhosis[23]. Whether genotype 3 causes more rapid fibrosis in comparison to other genotypes has not been clearly documented in appropriately designed comparative studies. However, from cross-sectional studies, indications are that genotype 3 may indeed cause more progressive disease[23]. The DAAs, particularly sofosbuvir with ribavirin therapy in genotype 3 with significant fibrosis have been reported to have a poorer response than in genotypes 1, 2, 4 and 6[24]. Therefore, unlike earlier years when genotype 1 HCV was considered to be difficult to treat with interferon and ribavirin, it seems that genotype 3 HCV associated with fibrosis is difficult to treat with DAA.

The most common sources of infection were blood transfusion in 50 per cent patients and iatrogenic in 25 per cent of patients. In another 22 per cent of our patients, the source of infection was not clear, and likely resulted from the unsterile injection practices. At least 50 per cent of injections administered in the developing world were found to be unsafe and at risk of transmitting infections in a previous study[25]. In a community-based study from West Bengal, India, the odds ratio to acquire HCV infection by using reusable glass syringes was 3.82[26]. Further, it is also well known that progression of the liver disease in transfusion associated HCV infection is more rapid than in patients who acquire HCV through other sources[27].

Despite the fact that the present study included patients with significant fibrosis (>F2) in 35.8 per cent, the overall SVR rate was 64 per cent. Similar SVR rates were seen in genotype 3 and predominantly genotype 1 patients. Similar response rates have been documented in various clinical trials reported from West[2,4]. Another study from north India also reported a similar response rate[28], whereas a recent study describing real life scenario reported SVR rates of 78 per cent in genotype 3[28]. The high SVR rates may be due to the fact that cirrhosis, which is an important predictor of response, was present in only 21 per cent of patients. A multicentre study from India which used regular interferon with ribavirin reported a SVR of about 65 per cent in CHC patients[29]. These studies would indicate that about 65 per cent of CHC patients in India could be treated effectively with interferon and ribavirin therapy. In view of availability of the DAAs now in India, addition of peg interferon to sofosbuvir and ribavirin is likely to further enhance the SVR in such patients. The higher SVR rates for genotype 1 may be due to low viral load and lesser degree of fibrosis which has also been observed in previous studies[28,29].

Multivariate analysis revealed BMI ≥ 23 kg/m^2, HOMA-IR ≥ 2, compliance (≤80%) and significant fibrosis on biopsy were independently associated with a lower SVR. This finding is interesting as Indians are known to have proneness to develop insulin resistance (IR) with mild weight gain[30]. In a population based study conducted in rural India, a BMI > 18 kg/m^2 was

progressively associated with IR[30]. A similar report has also been published from USA in which Indians staying in USA were documented to have higher IR than other races with similar BMI[31]. Among these predictive factors, two factors (BMI and HOMA-IR) are modifiable and can be altered by dietary and lifestyle modifications. Further study is needed to document whether by controlling these modifiable factors the SVR can be further improved in Indian patients with genotype 3 infection.

Overall the combination therapy with peginterferon and RBV was well tolerated in CHC patients. Majority of patients (90%) had good compliance. One third of the patients had low counts and required the use of growth factors. The use of growth factors did not influence the SVR rates.

This study was limited by the fact that some of the data were collected retrospectively and hence all the predictive factors were not available in all patients. The strength of the study was that it assessed the real life SVR in Indian patients. Moreover, the predictive factors of response were analyzed in a systematic manner in all the genotypes.

In conclusion, combination therapy with peginterferon and ribavirin demonstrated good tolerability in treatment-naïve patients with CHC. Prior blood transfusion and surgery still remain the most common source of infection. Genotype 3 was found to be the most prevalent genotype in India followed by genotype 1. In comparison to the western population, genotype 1 had better and genotype 3 had poorer SVR rates in our study population, both in chronic hepatitis and cirrhosis patients. Higher SVR for genotype 1 in comparison to western report is probably due to low viral load and less advanced disease[4,12]. BMI $\geq$ 23 kg/m^2, HOMA-IR $\geq$ 2, compliance ($\leq$80%), significant fibrosis (>F2) were predictive of low SVR. The baseline viral load and genotype did not predict response.

***Conflicts of Interests*:** None.

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Reprint requests: Dr Subrat Kumar Acharya, Room No 3105, 3rd Floor, Teaching Block, Department of Gastroenterology, All India Institute of Medical Sciences, New Delhi 110 029, India
e-mail: subratacharya@hotmail.com