Original Article

Treatment results and factors affecting sustained virological response in chronic hepatitis C patients in Northern India

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ABSTRACT

Background and Objectives: Chronic hepatitis C (CHC) is a major cause of liver-related morbidity and mortality. Data on the treatment outcomes of CHC with pegylated interferon plus ribavirin (PEG-RBV) in Indian patients are limited. This study aimed to evaluate the efficacy, safety and factors associated with sustained virological response (SVR) in CHC patients treated with PEG-RBV in northern India. **Materials and Methods:** Consecutive treatment naïve patients with CHC infection treated with PEG-RBV combination therapy between January 2011 and December 2014 were included. Patients with cirrhosis and other contraindications were excluded. **Results:** Of the total 108 patients enrolled, 102 (94.4%) patients completed the treatment (mean age- 43 ±12.7 years; 62% males). The mean BMI was 23.9 ± 4.2 and mean ALT was 85.7 ± 68 IU/L. HCV viral load >4,00,000 IU/ml was present in 45.4%. The most common genotype was 3 (69.4%; n=75), followed by genotype 1 (26.8%; n=29) and genotype 4 (3.7%; n=4). By intention-to-treat analysis, the overall SVR rate was 94.4% (102/108). In genotype 1 patients it was 86.2% (25/29) and 98.7% (74/75) (p=02) in genotype 3 patients. On multivariate analysis, non-genotype 3 infection predicted lower SVR. **Interpretation and Conclusions:** SVR rates in CHC patients treated in northern India with PEG-RBV therapy in our study (86.2% for genotype 1 and 98.7% in genotype 3) were better than those reported in western and other Indian studies. Better patient compliance, better monitoring and better management of adverse events lead to superior treatment outcomes.

Keywords: Chronic hepatitis C, pegylated interferon, ribavirin

INTRODUCTION

Chronic hepatitis C (CHC) infection affects approximately 170 million people worldwide and is a major cause of liver related morbidity and mortality.[1] In India, an alarmingly high prevalence rate of CHC (5.8%) has been reported from Punjab, northern India.[2] A significant proportion of patients with CHC may develop cirrhosis, liver decompensation and hepatocellular carcinoma.[1,3] Treatment with anti-viral therapy and achievement of sustained virological response (SVR) (defined as HCV RNA negativity after 6 months of treatment) prevents long term complications. In the last decade, combination therapy of pegylated interferon-alpha and ribavirin (PEG-RBV) has been the standard of care for treatment of CHC, which yielded SVR rates of 42-46% in genotype 1, and 76-82% in genotype 2/3 treatment-naive patients.[4-8] The better understanding of the HCV genomic structure, life cycle and the key viral enzymes has led to the development of Directly Acting Anti-virals (DAAs) which hold promise for the future. Addition of these agents to the standard of care consisting of PEG-IFN and RBV led to a significantly higher SVR rates in both treatment-naïve and treatment-experienced patients. In treatment-naïve CHC patients, an approximate 30% increase in SVR rates was achieved with the addition NS3/4A protease inhibitors like telaprevir, boseprevir, simeprevir or a NS5A inhibitor daclatasvir.[9] The NS5B polymerase inhibitor sofosbuvir, which has recently become

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available in the Indian sub-continent leads to approximately 40% increase in SVR when added to PEG-RBV therapy, as reported in the western literature.[10]

PEG-RBV combination still remains the backbone of the current treatment regimens including DAAs. It is important to know the treatment results and the factors associated with SVR with the existing PEG-RBV therapy to better understand the benefit and response rates of the newer therapies in the Indian population. Current treatment recommendations for CHC patients are mostly derived from randomized clinical trials, based on highly selected patient populations, without clinically significant co-morbidities, and under strict monitoring that is not feasible in routine clinical practice. Treatment results of CHC from the Indian subcontinent, where virus and disease characteristics, and health-care set-up are different from western countries, are scarce.[11-13] We performed this study to evaluate the efficacy and safety of PEG-IFN and RBV combination therapy, and to identify factors associated with SVR in a cohort of CHC patients treated in a 'real-life' setting in northern India.

MATERIALS AND METHODS

All treatment naïve patients with hepatitis C virus (HCV) infection treated with anti-viral therapy (PEG-IFN plus RBV) between July 2011 and June 2014 (3 years) were included in this retrospective analysis. Exclusion criteria were evidence of liver cirrhosis, co-infections with HBV or HIV viruses, history of previous antiviral or immuno-modulatory therapy, patients having contraindications for anti-viral therapy i.e. decompensated liver disease, active alcohol or drug abuse, major neuro-psychiatric illness, uncontrolled thyroid disorder or uncontrolled diabetes, autoimmune diseases, advanced cardio-pulmonary disease, renal failure, hemoglobin <12 g/dl (females) or <13g/dl (males), platelet count <90,000/mm^3 or neutrophil count <1500/mm^3 and were not offered anti-viral treatment.

A detailed history and clinical examination was undertaken. Baseline laboratory work-up included hemogram, liver and renal function tests, thyroid function tests, prothrombin time index (PTI), fasting blood sugar, α-feto protein and ultrasound abdomen. Cirrhosis was diagnosed on the basis of clinical, laboratory, radiological, endoscopic, and/or transient elastography (TE) criteria. TE was performed using Fibroscan (Echosens, Paris, France) and results were expressed as Kilo Pascals. TE measurement was considered valid if 10 measurements were obtained with a success rate of >60% and an interquartile range <30% of the median. TE value >11.7 was taken as the cut-off for cirrhosis (≥ F4). Increased alanine aminotransferase (ALT) was defined as ALT levels >40 IU/L. All the patients were tested for HBsAg and HIV co-infections. Work-up for autoimmune and metabolic diseases was done, where indicated. Anti-HCV antibody positivity was confirmed by ELISA (ELISCAN HCV; RFCL limited, Dehradun, India). HCV Ribo-Nucleic Acid (RNA) was quantified by real time polymerase chain reaction technology (COBAS Taqman HCV TEST 2.0; Roche Diagnostics Corporation, Indiapolis, IN, USA). High viral load was defined as HCV RNA >4,00,000 IU/ml.[1]

HCV genotype was also determined in all patients using the following method- HCV RNA was extracted from plasma or serum samples using QiaSymphony DSP Virus/pathogen kit on the Qiagen Qiasymphony platform. The extracted RNA was used for reverse-transcription-amplification by utilizing the one-step RT-PCR enzyme AgPath ID from Invitrogen (California). The target region for genotyping was selected as ~245 bp region of the 5'UTR. Sequencing was performed on ABI 3500DX system using BDT 1.1. The genotype was elucidated by posting the sequences into the HCV database (Los Alamos National Laboratory; http. hcv.lanl.gov/content/sequence/ Basic_Blast/basic_blast. html).

Patients were treated with PEG-IFNα2a (180 μg per week) or PEG-IFNα2b (1.5 μg/kg per week) subcutaneously plus ribavirin 800-1200 mg/day orally, according to body weight (<65 kg, 800 mg/day; 65-85 kg, 1000 mg/day; >85 kg, 1200 mg/day). The dose of each study medication was based on the patient's weight at the initiation of the therapy. Patients with HCV genotype 1 were treated for 48 weeks and genotype 3 for 24 weeks. All patients were then followed for additional 24 weeks to assess SVR. Treatment was considered to be 'complete' if the patient received >80% dose of both the treatment drugs for >80% of the recommended duration. Dose adjustments for adverse effects were made according to standard protocols. Antidepressants and growth factors (erythropoietin or granulocyte colony

stimulating factor) were used based on clinical condition of the patient or laboratory abnormalities.[14] Treatment was withdrawn prematurely by the treating physicians in case of non-response (HCV RNA positivity persisting after 24 weeks of therapy or viral load not decreasing by at least 2 log IU/ml after 12 weeks of therapy).

Patients were evaluated as outpatients for safety and efficacy at regular intervals. Routine hematology was assessed at 2 and 4 weeks, then every 4 weeks and whenever required. Liver biochemistry was monitored every 4 weeks and thyroid-stimulating hormone levels every 12 weeks during treatment. HCV RNA (quantitative) was repeated at 4 weeks for assessment of rapid virological response (RVR), at 12 weeks for detecting early virological response (EVR) (defined as HCV RNA negativity at 12 weeks), and at end of treatment (24 or 48 weeks depending on genotype) for end-of-treatment response (ETR- undetectable HCV RNA at the end of treatment). HCV RNA at 24 weeks of follow up was done for detecting SVR (defined as undetectable HCV RNA).

Non-responders were defined as patients who failed to achieve a decline of 2 log HCV RNA IU/ml after 12 weeks of treatment or who never achieved undetectable HCV RNA during treatment of a minimum duration of 24 weeks. *Relapsers* were defined as patients who achieved an ETR but subsequently relapsed and did not achieve an SVR.

Study outcome measures and endpoints

The primary outcome measure was the proportion of patients achieving SVR. The secondary outcome measures were the proportion of patients who achieved RVR, EVR and ETR. The primary endpoint of the study was completion of 24 weeks of follow up after completion of full recommended therapy. Secondary end-points were premature withdrawal of treatment in non-responders or in patients with severe side effects, or patient being lost to follow up. Safety and tolerability were assessed by monitoring adverse events (influenza-like symptoms, gastrointestinal, respiratory, dermatological, neuropsychiatric side effects etc.) and laboratory abnormalities (anemia, leucopenia/ neutropenia, thrombocytopenia) when they were reported during the treatment.

Statistical analysis

All data were analyzed using SPSS software package. Continuous data were expressed as mean ±SD. Categorical data were expressed as number/proportion of subjects with a specific feature. Chi-square test was used to compare categorical data. Analysis was performed on an 'intention to treat' basis. Multivariate logistic regression was performed to identify independent predictors of SVR, considering them as the dependent variables. A two-tailed p value of less than 0.05 was required for statistical significance.

RESULTS

Of the total 108 patients enrolled, 103 (95.4%) patients completed the planned duration of therapy and follow-up. Four patients were lost to follow up and treatment was stopped in one patient due to non-response. The mean age was 43 ± 12.7 years and 62% (n=67) were males. The mean BMI was 23.9 ± 4.2, and 39.8% (n=43) had BMI >25. The mean ALT was 85.7 ± 68 IU/L, and 87.9% (n=95) had elevated ALT (>40 IU/L). HCV viral load >4,00,000 IU/ml was present in 45.4% (n=49). Co-morbidities were present in 23.1% (n=25) [diabetes mellitus in 12.9% (n=14), hypertension in 9.2%

Table 1
Baseline characteristics of chronic hepatitis C patients (n=108)

Parameters	Values
Age (years)	43 ± 12.7
Age >40 years	41.7% (45)
Males (%)	62% (67)
Weight (kg)	70.3 ± 12.5
BMI	23.9 ± 4.2
BMI >25	39.8% (n=43)
ALT (IU/L)	85.7 ± 68
ALT >40 IU/L	87.9% (n=95)
HCV RNA >4,00,000 IU/ml	45.4% (n=49)
Presence of any co-morbid condition*	23.1% (n=25)
History of significant alcohol use	12% (13)

Data are expressed as mean ± S.D. or percentage (number). ALT, Alanine transaminase; BMI, Body mass index; HCV RNA Hepatitis C virus ribonucleic acid. *Comorbidities – diabetes mellitus (12.9%), hypertension in 9.2%, cardio-vascular disease (0.9%) and respiratory diseases (0.9%).

Table 2
Comparison of virological response in various HCV genotypes

Genotypes	RVR n (%)	EVR n (%)	ETR n (%)	SVR n (%)
1 (n=29)	26 (89.7%)	28 (96.6%)	26 (89.7%)	25 (86.2%)
3 (n=75)	73 (97.3%)	75 (100%)	74 (98.7%)	74 (98.7%)
4 (n=4)	3 (75%)	3 (75%)	3 (75%)	3 (75%)
Total (n=108)	**102 (94.4%)**	**106 (98.1%)**	**103 (95.4%)**	**102 (94.4%)**

ETR, end of treatment response; EVR, early virological response; RVR, rapid virological response; HCV, hepatitis C virus; SVR, sustained virological response

(n=10), cardio-vascular disease 0.9% (n=1) and respiratory diseases 0.9% (n=1)]. Baseline characteristics of the patients are shown in Table 1.

Majority of the patients had genotype 3 (69.4%; n=75), followed by genotype 1 (26.8%; n=29) and genotype 4 (3.7%; n=4). In the 'intention to treat' analysis, the overall SVR rate was 94.4% (102/108). The SVR rate was 86.2% (25/29 in genotype 1 patients), while it was 98.7% (74/75) (p=0.02) in genotype 3 patients. In the per-protocol analysis, the SVR rate was 100% (74/74) among genotype 3 patients and 96.2% (25/26) among genotype 1 patients. The virological response rates (ITT analysis) according to genotype are shown in Table 2. Besides the 4 patients lost to follow up (three of genotype 1 and one of genotype 3), one patient with genotype 4 had non-response to treatment, and one patient with genotype 1 had relapse. The ALT levels (biochemical response) was as follows: genotype 1 patients ALT levels decreased 92.4 ± 75 at baseline to 37.5 ± 24 at end of therapy; and in genotype 3 patients ALT levels decreased 79.7 ± 66 at baseline to 33.4 ± 19 at the end of therapy.

The various treatment related adverse events noted in our study are shown in Table 3. Ribavirin dose modification was required in 25% (n=27) patients and PEG-IFN dose modification in 22.22% (n=24) patients, and both in ten patients. Erythropoietin supplementation was required in 20.37% (n=22), GM-CSF in 2.7% (n=3) and blood transfusion in 1.8% (n=2) patients.

Table 3
Adverse events with pegylated interferon and ribavirin therapy (n=108)

Adverse events	%age (number)
Fatigue	82.4% (89)
Pyrexia	72.2% (78)
Myalgia	71.3% (77)
Anorexia	71.3% (77)
Weight loss	63.9% (69)
Nausea	55.6% (60)
Alopecia	41.7% (45)
Headache	28.7% (31)
Depression	24.1% (26)
Cough	22.2% (24)
Breathlessness	19.4% (21)
Thyroid dysfunction	11.1% (12)
Arthralgia / Arthritis	10.2% (11)
Hearing Disturbance	0.9% (1)
Hematological	
Anemia - hemoglobin <10 g/dl	25% (27)
Hemoglobin <8 g/dl	5.5% (6)
Neutropenia (<3000/mm3)	3.7% (4)
Platelet count (<50,000/mm3)	1.8% (2)

Factors associated with SVR

The baseline patient and viral related factors that were evaluated for their association with SVR were: sex, age, BMI, ALT, HCV genotype, HCV viral load, past alcohol use, co-morbidities and diabetes mellitus. On univariate analysis, factors significantly associated with SVR were age <40 years (p=0.004) and genotype 3 (p<0.001). On multivariate analysis, genotype 3(p<0.001) was found to be significantly associated with SVR**.**

The treatment related factors that were evaluated for their potential association with SVR were: RVR, EVR, hemoglogin decrease during treatment, ribavirin dose and PEG-IFN dose. On univariate and multivariate analysis, none of these factors were significantly associated with SVR.

DISCUSSION

This study evaluated the efficacy of PEG-IFN and RBV combination therapy and the factors affecting response to therapy in a cohort of CHC patients treated in a 'real-life' setting. Most of the available data on CHC treatment is derived from randomized clinical trials (RCTs) which are based on highly selected patient populations. Although RCTs are regarded as the reference standard for assessing the efficacy of treatment protocols, they are generally conducted under ideal conditions which are difficult to achieve in the routine clinical practice. Due to the variations in disease spectrum, disease severity, patient's socio-economic status, and experience of clinicians, results from RCTs may not be applicable to general population. The main findings of our study were a good overall SVR rate of 94.4% in CHC treatment naive patients, with an SVR rate of 98.7% in genotype 3 patients and 86.2% in genotype 1 patients.

Genotype 3 was the most common genotype in this study. This is in concordance with the other reports from northern India, while genotype 1 has been reported to be the most common genotype from southern India.[15]

The overall SVR rate reported in the present study was higher than the SVR rates reported in the landmark RCTs on CHC treatment (54%-63%),[4-6] and other 'real life' patients (50.2%-64%).[7-16,17] The results are also better than those noted among patients treated in our center previously *i.e* from the year 2004 to 2010.[8] Better understanding of the disease by the patient, better patient compliance and better management of adverse events leading to minimum dropouts is the primary reason for better results in this study.

Comparison of the SVR rates among the genotype 3 and genotype 1 patients separately showed similar results. Among genotype 3 patients, the SVR rates seen in our study were higher than the previously reported SVR rates of 66-84% in most of the studies from the western world.[4-7, 16,17] Among the genotype 1 patients, a more marked difference in the SVR rates was noted. Most of the RCTs and 'real world' studies from the western world have reported lower SVR rates ranging from 37-52% in genotype 1 patients[4-7,16-17] while the SVR rates in genotype 1 patients in our study were significantly better (86.2%; p< 0.001).

Effect of ethnicity on the SVR rates has been earlier reported.[18-19] In a Canadian study, SVR was observed in 65% of the Asian patients, compared to 45% of Caucasians (p=0.0047).[19] The ethnic differences were independent of viral genotype and titer, pharmacological regimen, treatment adherence, BMI, age, and hepatic fibrosis. In this study, the benefit of Asian ethnicity on treatment response was mainly observed in genotype 1 patients (Asian 65% *vs* Caucasians 36%, *p*< 0.05); but not in genotype 3 (Asian–57% *vs* Caucasian–64%). The impact of ethnicity on treatment response may be related to host factors like genetic differences in immune regulation, different class II human-leukocyte antigen alleles, different pretreatment cytokine profiles and differences in the HCV-specific CD4 Th1 proliferative response.[19] In addition, an important factor leading to better SVR rates among Asian population may be the favorable IL28B polymorphisms seen in Asian population.[20]

In the present study, patients with cirrhosis were not included. Data from previous studies favors the use of a longer duration of therapy in cirrhotics. In genotype 3 cirrhotic patients, comparable SVR rates are achieved if treated for 36-48 weeks instead of the standard 24 weeks duration. Similarly, among genotype 1 patients, relapse rates among cirrhotics was significantly higher as compared to non-cirrhotics when treated for 48 weeks, thus emphasizing the need for extended therapy.

Various factors have been reported to affect the response to PEG-RBV therapy in CHC patients. These

include viral factors such as genotype 1 and high viral load; treatment related factors such as slow virologic response, reduction in PEG-IFN or RBV doses; and patient-related factors such as high BMI, advanced age, male gender, African-American ethnicity, advanced baseline liver fibrosis, alcohol intake, and lack of adherence to therapy.[6,11,17,21] Manns *et al*[21] noted significant correlation of age (younger, p <0.0001) and the absence of cirrhosis (p =0.07) with SVR [21]. The present study found that non genotype 3 significantly associated with poor SVR, as determined by the multivariate analysis. The drop-out rate in our study (3.7%) was lower to that reported in other real-world studies (5-8%). This is one of the factors leading to better results in our study.

Although PEG-RBV therapy has been the standard of care in the last decade, there are chronic HCV patients who cannot be treated with PEG-IFN and RBV for several reasons. First and of most clinical relevance, PEG-IFN therapy is contraindicated in patients with decompensated liver disease. Second, patients may not tolerate and/or may have other contraindication(s) to treatment with PEG-IFN or RBV. So, there is a definite need for new antiviral drugs with better efficacy, improved tolerance and good safety profiles for the treatment of chronic HCV infection. The major drawback of the newer therapies for CHC is the high cost and limited availability in the initial phase especially in the developing countries, which may limit their use. For example, sofosbuvir became available in India at a reasonable cost only after a long period of being approved by the FDA. Till other newer therapies with interferon free regimens are available in the coming years, PEG-IFN and RBV will continue to be the backbone of CHC treatment. So, physicians should be confident in treating patients with interferon based therapies which can also lead to extremely good SVR rates as shown in this study.

Our study has few limitations. First, IL28B testing was not done in all the patients. However, as most of the patients were genotype 3, in which IL28B does not help predict the treatment response, this would not have added to the benefits of the study. To conclude, the SVR rates in CHC patients treated in real-life setting in northern India in the recent past were better than those reported previously in the western and Indian populations. This difference was more significant among genotype 1 patients (p<0.001). Better patient compliance, better monitoring and better management of adverse events lead to superior treatment outcomes. These results would give more confidence in treating patients with PEG-RBV therapy, and would also be important in planning and comparing future therapies in which newer directly acting anti-virals are added to the existing PEG-RBV therapy.

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Dept of Gastroenterology, DMCH, Ludhiana

CONFLICT OF INTEREST : None declared

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