Clinical Profile and Response to Treatment with Pegylated Interferon α 2b and Ribavirin in Chronic Hepatitis C—A Reappraisal from a Tertiary Care Center in Northern India

Vinod K. Dixit, Jayanta K. Ghosh, Sangey C. Lamtha, Pankaj Kaushik, Sundeeep K. Goyal, Manas K. Behera, Neha Singh, Ashok K. Jain

Department of Gastroenterology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh 221005, India

Aim: To assess the clinical profile of 80 chronic hepatitis C patients in a tertiary health care center in Northern India and also to study the efficacy and tolerability of pegylated interferon (Peg-IFN) α 2b and ribavirin therapy in a cohort of chronic hepatitis C patients. **Methods:** Thirty subjects with chronic hepatitis C (CH-C) with genotypes 2 and 3 received Peg-IFN α 2b 1.5 μ g/kg subcutaneously weekly plus daily ribavirin 800 mg for 24 weeks. Subjects with genotype 1 infection received therapy for 48 weeks with ribavirin 1000 mg/day and Peg-IFN α 2b dose remained the same. The primary end point was the sustained viral response (SVR). Drug dosage was modified or temporarily discontinued if anemia or bone marrow suppression developed. **Results:** The clinical profile of chronic hepatitis C infected patients showed decompensated cirrhosis in the more elderly patients. Genotype 3 was the commonest genotype and was seen in 21 (70%) patients. The mean baseline HCV RNA was high. SVR was achieved less commonly with genotype 1 than with genotype 2/3. Patients who became negative for HCV RNA at 4-weeks (rapid virological response or RVR) and 12 weeks (early virological response or EVR) of treatment showed significantly higher sustained virological response (SVR) rates. Similarly, patients who showed normalization of ALT level at 4-weeks and 12-weeks of treatment showed significant high rate of SVR. Overall treatment was well tolerated. **Conclusion:** In our region, CHC subjects have high viral load and genotype 3 being the most common. Treatment with Peg-IFN α 2b and ribavirin is effective and well tolerated. Genotype 1 was more resistant to the treatment. Patients who achieved RVR and EVR are more likely to achieve SVR. Although the numbers of patients in this study was small, considering the paucity of data of treatment from India, the data is relevant. (J CLIN EXP HEPATOL 2014;4:101–105)

Chronic Hepatitis C (CH-C) continues to be a leading cause of chronic liver disease with 28% of cases of cirrhosis and 26% of cases of liver cancer globally.¹ The seroprevalence rate of HCV among the blood donor population in India is 1.8%–2.5% and HCV is the etiological agent in about 20% of patients with chronic hepatitis in northern India.^{2–7} Genotype 3 is the most prevalent genotype in India and despite the current

revolutionized international guidelines based on oral direct acting antivirals (DAA) for managing chronic HCV infection, combined interferon and ribavirin still remains a viable and standard therapeutic option in India due to financial constraints. Sustained virological response (SVR) rates for genotype 1 HCV are approximately 40% following 48 weeks of pegylated interferon (Peg-IFN)/ribavirin and 80% or more in those with genotypes 2 and 3 infections according to western literature.^{8,9} The outcome of therapy depends on host factors (age, sex, body mass index, ethnicity, baseline alanine aminotransferase, IL-28B gene polymorphism and stage of liver disease), viral factors (pretreatment viral load, genotype) and compliance with therapy.⁹ Data is scarce in literature from this part of India regarding the treatment response with Peg-IFN α 2b and ribavirin in CH-C. The aim of this prospective study was to project the clinical profile, to assess treatment response with standard care of therapy in CH-C patients belonging to eastern part of North India and to evaluate the factors influencing the outcome.

Keywords: chronic hepatitis, genotype, hepatitis C virus, pegylated interferon, therapeutic response

Received: 8.4.2013; Accepted: 22.5.2014; Available online: 18.6.2014

Address for correspondence: Vinod K. Dixit, Professor, Department of Gastroenterology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh 221005, India. Tel.: +91 9415202449 (mobile)

E-mail: drvkdxit@gmail.com

Abbreviations: CBC: complete blood count; CH-C: chronic hepatitis C; DAA: direct acting antivirals; ETR: end of therapy; LFT: liver function test; Peg-IFN: pegylated interferon; RFT: renal function test; SVR: sustained viral response; TLC: total leukocyte count

<http://dx.doi.org/10.1016/j.jceh.2014.05.012>

MATERIAL AND METHODS

Eighty treatment naive patients with CH-C attending the Liver Clinic, Institute of Medical Sciences, Banaras Hindu University, Varanasi, from January 2011 to December 2012 were included in this prospective study. Institutional ethical committee approved the study protocol and informed consent was taken from patients. The baseline clinical features and investigations were recorded. Patients were divided into three groups: 1) CH-C infection (without any evidence of cirrhosis), 2) CH-C with compensated cirrhosis, and 3) CH-C with decompensated cirrhosis.

CH-C was diagnosed based on anti-HCV positivity for 6 months or more. Cirrhosis was diagnosed on the basis of clinical, biochemical, serological, ultrasonographic and endoscopic findings. Histology data was not available, as liver biopsy was not done in any patient.

All patients were further investigated for complete blood count (CBC), blood sugar, liver function test (LFT), renal function test (RFT), thyroid function test, serum ceruloplasmin, 24 h urinary copper and serum ferritin. Patients who were positive for HBsAg, HIV and autoimmune antibodies were excluded from the study. Patients with evidence of compensated or decompensated cirrhosis were not offered anti-HCV therapy. Thirty patients, who met the above criteria, received anti-HCV therapy. Information regarding drug dosages, duration, adverse effects, and total cost of therapy was given. All of the patients agreed for Peg-IFN and ribavirin based treatment. Sixteen patients arranged the cost of treatment themselves, while the other 14 patients got financial support through the state/central government.

Treatment Schedule

Peg-IFN α 2b, 1.5 μ g/kg once a week subcutaneously in combination with oral ribavirin 800 mg/day for genotypes 2, 3 and 1000 mg/day for genotype 1 into two divided doses were given. Patients with genotypes 2, 3 received treatment for 24 weeks and genotype 1 for 48 weeks duration. Patients were admitted for the first dose of Peg-IFN α -2b and observed for any adverse effects and discharged from the hospital after the 2nd dose of Peg-IFN α -2b. Thereafter patients were monitored on outpatient basis. Physical signs, CBC, LFT, RFT and drug compliance were monitored. Drug dosage was reduced if the hemoglobin level fell below 9 g/dL, and/or the total leukocyte count (TLC) dropped below 3000/mm³ and/or the platelet count fell below 75,000/mm³, and therapy was temporarily stopped if the corresponding values were less than 7 g/dL, 2000/mm³ and 50,000/mm³, respectively. The primary end point was SVR (HCV RNA negativity at 24 weeks after therapy). Virologic responses were assessed at 4 weeks (RVR), 12

weeks (EVR), 24/48 weeks ETR (end of therapy) and 24 weeks after end of therapy (SVR). Virologic responses were defined as per AASLD guidelines.⁹

Statistical Analysis

Discrete variables were compared using χ^2 test with its correction factor. Continuous and rating variables were compared using Student's *t*-test and one-way ANOVA. An SPSS software package version 16.0 (Statistical Package of Services Solutions, SPSS, Chicago, IL, USA) was used to perform the statistical analysis. *P* < 0.05 was considered as statistically significant.

RESULTS

Thirty patients (37.5%) had CH-C infection without any evidence of cirrhosis, 29 (36.2%) patients had decompensated cirrhosis and 21 (26.2%) patients had compensated cirrhosis. The implicated source of infection was blood and blood product transfusion in 10 (33.3%), previous surgery in 5 (16.6%), tooth extraction, IV drug abuse, affected spouse (one each) and unknown in 12 (40%). Mean age was highest in decompensated cirrhosis (49.9 years) followed by compensated cirrhosis (45.3 years) and lowest in chronic hepatitis (40.8 years). Other baseline characteristics i.e. body mass index, ALT, albumin, hemoglobin, TLC and platelet count in these three groups are depicted in Table 1. The baseline HCV RNA quantitation was done in CH-C patients without any evidence of cirrhosis and the median baseline quantitative HCV RNA in these subjects was 156,720 IU/ml (range: 8250–9,900,000 IU/ml). Since the data was skewed hence median was calculated rather than mean.

Among the 30 patients with CH-C infection, genotype 1 was detected in 5 patients (16.6%), genotype 2 in 4 patients (13.3%) and genotype 3 in 21 patients (70%). SVR (HCV RNA negativity 24 weeks after end of therapy) was significantly higher in subjects achieving EVR (HCV RNA negativity at 12 weeks of therapy) (86.9% vs 14.3%) and RVR (HCV RNA negativity at 4 weeks of therapy) (89.5% vs 36.4%) (Table 3). Among the 30 patients with CH-C 21 (70%) patients achieved SVR. Patients with genotype 1 achieved significantly lower SVR (20.0%) as compared to genotype 2/3 (92.0%). We also found an association of early normalization of ALT level with SVR. The proportion of patients with normal ALT level at the end of 4 and 12 weeks of treatment was significantly higher in those with SVR than in those without SVR (Table 3). The baseline mean age, BMI, SGPT, hemoglobin, TLC, platelet count did not show any significant difference among the SVR and non-SVR groups (Table 2). The baseline mean HCV RNA was more in non-SVR group although statistically it was not significant (Table 2).

Table 1 Baseline Characteristics of Chronic Hepatitis C Patients (n = 80).

Variable	Chronic hepatitis C infection (n = 30) (no evidence of cirrhosis)	Compensated cirrhosis (n = 21)	Decompensated cirrhosis (n = 29)	P-value
Age (year)	40.81 ± 12.63 ^a	45.32 ± 8.05	49.92 ± 11.69	0.01
BMI (kg/m ²)	23.56 ± 2.59	23.15 ± 3.42	22.76 ± 2.73	0.56
ALT (U/L)	91.83 ± 45.78	57.82 ± 22.82	40.50 ± 21.32	0.001
Albumin (g/dL)	3.98 ± 0.73	3.04 ± 0.57	3.00 ± 0.73	0.001
Hemoglobin (g/dL)	12.99 ± 1.79	10.25 ± 2.7	10.64 ± 1.84	0.01
TLC (× 1000 mm ⁻³)	8.51 ± 2.63	10.33 ± 7.49	7.26 ± 3.58	0.09
Platelets (× 10 ⁵ mm ⁻³)	2.32 ± 0.46	1.12 ± 0.49	1.01 ± 0.33	0.001
HCV RNA (IU/mL)	156,720 (range: 8250–9,900,000) ^b	Not done	Not done	Not done

ALT, alanine amino transferase, TLC, total leukocyte count.

^aMean ± standard deviation.

^bMedian (range).

Common side effects were bone marrow suppression (neutropenia, thrombocytopenia), ribavirin related anemia, mood depression etc. Dose modifications were done in case of severe adverse reactions. However, all the patients tolerated the therapy well. Treatment was not stopped in any of the patients.

DISCUSSION

The study clearly reveals that hepatitis C related liver diseases are not uncommon in our population. Its prevalence is nearly half to that of chronic hepatitis B related liver disorders as during study period of 2 years we recorded 80 patients with HCV related liver diseases compared to 182 patients with hepatitis B related liver diseases. However, many of them (50 out of 80) were presented in advanced stage of disease and not suitable for antiviral therapy or likely to have poor response. Several studies have looked at the prevalence of hepatitis C in chronic liver disease in India. The prevalence of hepatitis C has ranged from 10.8% to as high as 48.5%.^{2–5} In a report from Eastern India, Ray G and colleagues

showed 62 (35.4%) patients had HBV related chronic liver disease and 17 (14.9%) cases had HCV related chronic liver disease.⁸ In another study from Northern India by Sood A et al in 1999, sixteen (18.8%), 22 (25.9%) and 21 (24.7%) patients had HBV, HCV and HBV + HCV infection, respectively.⁹ As the disease advances, liver fibrosis also progresses, and transaminases, albumin and platelets gradually decrease with disease progression. Progression of fibrosis can be accelerated by factors such as older age, duration of HCV infection, sex, and alcohol intake.¹⁰

Great majority (70%) of our subjects were infected with genotype 3 HCV and about a sixth each belonged to genotype 1 and 2. There are many previous reports from different regions of India on genotype prevalence. In most of the studies, genotype 3 was overall more common in Northern, eastern and Western parts of India, but patients from South India are predominantly infected with genotype 1.^{11–15} In contrast, most of the studies from USA, Europe and Japan have reported a prevalence rate of 60%–70% of genotype 1b and 1a in patients with CH-C.¹⁶

Table 2 Baseline Parameters in SVR (n = 21) and No SVR (n = 9) Patients.

Variable	SVR	No SVR	P-value
Age (year)	40.86 ± 12.70 ^a	40.67 ± 13.25	0.971
BMI (kg/m ²)	24.13 ± 2.43	22.48 ± 2.88	0.118
ALT (U/L)	95.51 ± 47.73	83.11 ± 42.19	0.677
Hb (g/dL)	12.90 ± 1.51	13.21 ± 2.42	0.675
TLC (× 10 ³ mm ⁻³)	8.681 ± 2.324	8.122 ± 3.373	0.603
PLT (× 10 ⁶ mm ³)	2.28 ± 0.46	2.35 ± 0.51	0.691
HCV RNA (IU/ml)	152,669 (range:8250–8,006,120) ^b	185,860 (range: 12,000–9,900,000)	0.542

SVR, sustained viral response; BMI, body mass index; TLC, total leukocyte count; PLT, platelets.

^aMean ± standard deviation.

^bMedian (range).

Table 3 Univariate Analysis of Factors Associated with SVR.

Variable	SVR	No SVR	P-value
Non-alcoholic	17 (77.3%)	5 (22.7%)	0.195
Alcoholic	4 (50.0%)	4 (50.0%)	
Rural	9 (81.8%)	2 (18.2%)	0.419
Urban	12 (63.2%)	7 (36.8%)	
Platelets < 2 lac/mm ³	8 (72.7%)	3 (27.3%)	0.571
≥2 lac/mm ³	13 (68.4%)	6 (31.6%)	
Genotype 1	1 (20.0%)	4 (80.0%)	0.004
Genotype 2, 3	23 (92.0%)	2 (8.0%)	

SVR, sustained viral response.

HCV treatment responses vary with the genotype, with the highest SVR rates observed for genotype 2, 3 (72–80%) and the lowest rates observed for genotypes 1 and 4 (44–50%).^{13,17–19} Our study population also showed similar results as genotype 1 (20%) had significantly low SVR as compared to genotype 3/2 (92.0%).

Patients in whom SVR couldn't be achieved had higher viral load as compared to them who achieved SVR. Most of the previous reports found that viral load is an important determinant of therapeutic outcome and patients with high viral load have been generally associated with a poor response.^{21–23}

Nineteen patients had achieved RVR. Seventeen of these 19 patients (89.5%) had finally achieved SVR. Rest of the 11 patients who did not achieve RVR, among them only 4 (36.4%) had achieved SVR ($p = 0.004$). Similarly, 23 patients had achieved EVR, out of which 20 (86.9%) had achieved SVR. Whereas, rest of the 7 patients who did not achieve EVR, only 1 (14.3%) had achieved SVR ($p = 0.001$). So, RVR and EVR were come out to be important determinants for predicting SVR in this study. Similar results have been published in previous Western and Indian studies.^{24,25}

Eighteen patients had normal ALT level at 4 weeks of treatment, among them 16 (88.9%) achieved SVR. On the other hand 12 patients had elevated ALT level at 4 weeks of treatment however, only 5 (41.7%) could achieve SVR and the difference was statistically significant ($p = 0.013$). Similarly, 19 patients had normal ALT level at 12 weeks of treatment out of which 17 (89.5%) patients had achieved SVR, while 11 patients had elevated ALT level at 12 weeks of treatment and only 4 (36.3%) patients had achieved SVR. The difference was again statistically significant ($p = 0.004$). So, in present study normalization of ALT at 4 weeks and 12 weeks corresponded to higher SVR rates. Similar findings were earlier reported in another Indian study.¹³

Therapy was generally well tolerated except for the development of reversible dose dependent bone marrow suppression and ribavirin-induced anemia. The primary management of hematological side effects during treat-

ment for hepatitis C, as recommended in the package inserts is the reduction of the dose of Peg-IFN or Ribavirin.²⁶ Ribavirin was reduced to a dose of 600 mg/day in three patients (all were genotype 3) for severe anemia and erythropoietin was given at a dose of 4000 IU/week throughout the antiviral therapy. Nine patients had developed neutropenia. Granulocyte-Monocyte stimulating factor (GM-CSF) was given to all of them one day prior to next Peg-IFN injection throughout their antiviral therapy. None of the patients required any specific therapy for thrombocytopenia. However, none of them required discontinuation of therapy for these adverse effects. Although erythropoietin is not approved by the FDA for the treatment of anemia among patients undergoing hepatitis C treatment, this strategy is employed in clinical practice worldwide.^{27,28} The dose of Peg-IFN should be reduced when the absolute neutrophil count is less than 750/ μ L and stopped when it is less than 500/ μ L.²³ A small clinical trial has demonstrated that GM-CSF can be used to stimulate neutrophil production in patients receiving interferon.²⁹

The main limitation of our study was the small patient number, which reduces the impact of significance tests and lack of histological data. Nevertheless, this prospective study reconfirms the efficacy, safety and factors determining outcome of therapy in a tertiary care center in this part of India, where the disease prevalence is now recognized to be greater than it was believed earlier. CH-C is now being detected at a rate higher than earlier due to increased awareness among patients and physicians, easy availability of screening tests at blood banks, airports and laboratories.

In conclusion, our study shows that patients with CH-C coming to this Institute in North India were predominantly infected with genotype 3 HCV and had a high viral load. The predominant source of infection in these patients was largely unknown followed by blood transfusion. Genotype 1 had lower SVR than genotype 2/3. Patients who achieved RVR and EVR had higher SVR. Similarly, patients who had early normalization of ALT had higher SVR. The efficacy and tolerability of combination of Peg-IFN α 2b and Ribavirin therapy in patients of chronic hepatitis C in this part of India was encouraging, in spite of high viral load, and the results were more or less similar to that seen in rest of India and in the West.

CONFLICTS OF INTEREST

All authors have none to declare.

REFERENCES

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2095–2128.
2. Mukhopadhyaya A. Hepatitis C in India. *J Biosci*. 2008;33:465–473.

3. Amarapurkar DN, Kirpalani A, Amarapurkar A, Kankonkar S. Prevalence of hepatitis C genotypes in Indian patients and their clinical significance. *J Assoc Physicians India*. 2001;49:983–985.
4. Sarin SK, Banerjee K, Khandekar P. Low prevalence of hepatitis C viral infection in patients with non-alcoholic chronic liver disease in India. *J Assoc Physicians India*. 1996;44:243–245.
5. Issar SK, Ramakrishna B, Christopher S, Samuel BU, John TJ. Prevalence and presentation of hepatitis C related chronic liver disease in southern India. *J Trop Med Hyg*. 1995;98:161–165.
6. Ray G, Ghoshal UC, Banerjee PK, et al. Aetiological spectrum of chronic liver disease in eastern India. *Trop Gastroenterol*. 2000 Apr-Jun;21(2):60–62.
7. Sood A, Sidhu SS, Midha V, Jyoti D. High seroprevalence of hepatitis C virus and dual infection (hepatitis B and C virus) in non-alcoholic chronic liver disease in north India. *J Assoc Physicians India*. 1999;47(2):205–208.
8. Hoofnagle JH, Seeff LB. Peginterferon and ribavirin for chronic hepatitis C. *N Engl J Med*. 2006;355:2444–2451.
9. Strader DB, Wright T, Thomas DL, Seeff LB. American Association for the Study of Liver Diseases. Diagnosis, management and treatment of Hepatitis C. *Hepatology*. 2004;39:1147–1171.
10. Jacobson IM, Davis GL, El-Serag H, Negro F, Trépo C. Prevalence and challenges of liver diseases in patients with chronic hepatitis C virus infection. *Clin Gastroenterol Hepatol*. 2010;8(11):924–933.
11. Chowdhury A, Santra A, Chaudhuri S, et al. Hepatitis C virus infection in the general population: a community based study in West Bengal, India. *Hepatology*. 2003;37:802–809.
12. Panigrahi AK, Roca J, Acharya SK, Jameel S, Panda SK. Genotype determination of hepatitis C virus from northern India: identification of a new subtype. *J Med Virol*. 1996;48:191–198.
13. Hazari S, Panda SK, Gupta SD, Batra Y, Singh R, Acharya SK. Treatment of hepatitis C virus infection in patients of northern India. *J Gastroenterol Hepatol*. 2004;19:1058–1065.
14. Raghuraman S, Shaji RV, Sridharan G. Distribution of the different genotypes of HCV among patients attending a tertiary care hospital in south India. *J Clin Virol*. 2003;26:61–69.
15. Narahari S, Juwle A, Basak S, Saranath D. Prevalence and geographic distribution of Hepatitis C Virus genotypes in Indian patient cohort. *Infect Genet Evol*. 2009 Jul;9(4):643–645.
16. Martinot-Peignoux M, Roudot-Thoraval F, Mendel I, et al. Hepatitis C virus genotypes in France: relationship with epidemiology, pathogenicity and response to interferon therapy. The GEMHEP. *J Viral Hepat*. 1999;6:435–443.
17. Hadziyannis SJ, Sette Jr H, Morgan TR, et al. Peginterferon- α 2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med*. 2004;140:346–355.
18. Hansen N, Obel N, Christensen PB, et al. Effectiveness of treatment with pegylated interferon and ribavirin in an unselected population of patients with chronic hepatitis C: a Danish nationwide cohort study. *BMC Infect Dis*. 2011;11:177.
19. Ray G, Pal S, Nayyar I, Dey S. Efficacy and tolerability of pegylated interferon alpha 2b and ribavirin in chronic hepatitis C – a report from Eastern India. *Trop Gastroenterol*. 2007;28:109–112.
21. Pereira LMMB, Spinelli V, Ximenes RA, et al. Chronic hepatitis C infection: influence of the viral load, genotypes, and GBV-C/HGV co-infection on the severity of the disease in a Brazilian population. *J Med Virol*. 2002;67:27–32.
22. Martinot-Peignoux M, Boyer N, Pouteau M, et al. Predictors of sustained response to alpha interferon therapy in chronic hepatitis C. *J Hepatol*. 1998;29:214–223.
23. Garg G, Kar P. Management of HCV infection: current issues and future options. *Trop Gastroenterol*. 2009;30(1):11–18.
24. Ferenci P. Predictors of response to therapy for chronic hepatitis C. *Semin Liver Dis*. 2004;24(suppl 2):25–31.
25. Duseja A, Choudhary NS, Gupta S, Chawla Y, Sakhuja V. Treatment of chronic hepatitis C in end stage renal disease: experience at a tertiary care centre. *Trop Gastroenterol*. 2012 Jul-Sep;33(3):189–192.
26. Nguyen DL, Morgan TR. Management of adverse Events during the treatment of chronic hepatitis C infection. *Clin Liver Dis*. April 2012;1(2).
27. Reddy KR, Shiffman ML, Morgan TR, et al. Impact of ribavirin dose reductions in hepatitis C virus genotype 1 patients completing peginterferon alfa-2a/ribavirin treatment. *Clin Gastroenterol Hepatol*. 2007;5:124–129.
28. Pfeffer MA, Burdmann EA, Chen CY, et al, for TREAT Investigators. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med*. 2009;361:2019–2032.
29. Van Thiel DH, Faruki H, Friedlander L, et al. Combination treatment of advanced HCV associated liver disease with interferon and G-CSF. *Hepatogastroenterology*. 1995;42:907–912.