ORIGINAL ARTICLE

RESPONSE TO STANDARD INTERFERON A2b AND RIBAVIRIN COMBINATION THERAPY IN CHRONIC HEPATITIS C TREATMENT NAÏVE PATIENTS

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Background: Treatment of Chronic Hepatitis C is now well established with conventional interferon or pegylated interferon in combination with ribavirin. Peginterferon Alfa and Ribavirin for 6 to 12 months is currently approved initial therapy, which is expensive. Response of our patients to standard Interferon-alpha-2b and ribavirin for 24 weeks have been studied. The objective of this study was to asses Sustained Viral Response (SVR) with standard Interferon A2b and Ribavirin combination treatment in chronic Hepatitis C patients. **Methods:** This quasi-experimental study was conducted at Combined Military Hospital, Quetta from Jan 2006 to Jun 2007. One hundred and three patients, with 20–60 years of age suffering from chronic Hepatitis C were selected on the basis of raised ALT, positive anti-HCV antibodies, evidence of viraemia by quantitative PCR for HCV RNA and liver biopsy. All patients were started on same brand of Interferon alpha-2b, 3 MIU subcutaneously, thrice weekly and oral Ribavirin (1,000–1,200 mg/day) for 24 weeks. End treatment response (ETR) after completion of treatment and SVR six months after ETR were recorded. **Results:** The 103 patients, 85 males and 18 females with mean age of 21–48 years completed the treatment for 24 weeks. Mean ALT was 96.17 (SD±49.98). End treatment response (ETR) was 89.3% (p=0.032). Sustained Viral Response after 6 months of treatment was 86.4% (p=0.034). **Conclusion:** Standard Interferon and Ribavirin had excellent SVR. It is effective as well as economical treatment in Chronic Hepatitis C patients.

Keywords: Chronic Hepatitis C, Interferon A2b, Ribavirin, SVR

INTRODUCTION

Hepatitis C virus (HCV) is an important causative agent of parenteral non-A-non-B hepatitis. Choo and co-workers of Chiron Co-operation Group discovered HCV as a new viral agent in 1989.[1] The World Health Organization estimates that approximately 3% of the world population has been infected with HCV. There are about 170 million patients with HCV worldwide and three to four million individuals are newly diagnosed each year.[2,3] In Pakistan, the prevalence of HCV varies widely, but generally is in the range of 3–13%.[4] It is estimated that approximately ten million people (6% of the population) have been living with HCV infection.[5]

Diagnostic test for chronic hepatitis C is persistently raised serum ALT levels; however it is non specific and is not a reliable indicator of the disease.[6] Elevated serum ALT levels indicate active disease of liver but 25% of chronic hepatitis C patients may have normal or widely fluctuating levels.[7] Serologic and nucleic acid-based molecular assays are available for the diagnosis of hepatitis C. Serologic tests are sufficient when chronic hepatitis C is expected, with a sensitivity of more than 99% in the 3rd generation assays. Positive serologic results require PCR in order to discriminate between chronic hepatitis C and resolved HCV infection from the past.[8] Liver biopsy, an invasive procedure though not necessary for diagnosis, but assess necroinflammatory damage to liver parenchyma and shows severity of the disease. Liver biopsies are scored by various scoring systems, e.g., Knodell Histopathological Index (HPI) based on inflammatory, necrotic and fibrotic changes.[9]

The treatment of CHC is now well established with conventional interferon or pegylated interferon in combination with Ribavirin.[10] Patients with chronic hepatitis C, response rates to interferon-based therapy are heterogeneous and in 'easy-to-treat' genotypes 2 and 3, SVR is observed in about 80% of patients with just 24 weeks of therapy, a lower dose of Ribavirin, and either standard interferon or peginterferon.[11]

The aim of this study was to determine the response of standard Interferon A2b and Ribavirin in Chronic Hepatitis C patients in our setup.

METHODOLOGY

This quasi-experimental study was conducted at Combined Military Hospital Quetta from Jan 2006 to Jun 2007. One hundred and three patients (80 males and 27 females) who were treatment naïve and non cirrhotic were included. Age ranges between 18–48 years were included by non-probability convenience sampling while reporting to outpatient department. Written informed consent was taken from all patients. Patients with persistently raised serum ALT (>42 IU/L), positive HCV antibodies by 3rd generation ELISA, positive HCV RNA by polymerase chain reaction by HCV Real-TM Quant SC were included. Liver biopsy compatible with

the diagnosis of chronic Hepatitis C on the basis of Knodell HPI scoring system was also done. Patients co-infected with HBV, decompensated cirrhosis, anaemia, other medical illnesses, depression and pregnancy were excluded from this study.

All patients were hospitalised for one to two weeks or longer if required to see safety and tolerance of treatment. After detailed history and physical examination, blood complete picture, liver function tests, coagulation profile and chest x-rays were done. Liver biopsy was done earlier with written consent after ultrasound marking and Knodell HPI was recorded. All patients were started on same brand of medicines with Injection Interferon (IFN) A2b (3 MIU subcutaneously, thrice weekly) and oral Ribavirin (1,000–1,200 mg/day) were given for 24 weeks. The medicines were provided free of cost by the institution. All patients were advised fortnightly regular follow up in out patient department. Biochemical and haematological profiles were done to see compliance and complications. After completion of treatment PCR for HCV RNA was done to see end treatment response (ETR) and six months later for sustained viral response (SVR) which is our primary end point.

Statistical analysis was done using SPSS-15. Descriptive statistics like mean and standard deviation was calculated for quantitative variables like age while frequency with percentages was used for qualitative data like gender, ETR and SVR. Chi-square test was applied to compare PCR findings. Statistical significance was determined at $p<0.05$ for all comparisons.

RESULTS

One-hundred-three treatment naïve patients completed the treatment for 24 weeks (Table-1). They were followed up for 6 months after treatment to see sustained viral response (SVR). Patients who declined to undergo treatment or follow up were excluded.

Eighty-five (82.5%) patients were males and 18 (12.5%) were females with age ranged from 21–48 years. The mean age was 31.75±5.87 years. ALT levels ranged from 44 to 385 U/L with mean value of 96.17±49.98.

Measurements of disease activity (grade) and fibrosis (stage) were calculated on liver biopsy by Knodell Histopathological Index (HPI) scoring system. Liver inflammation was graded as no inflammation (0) to minimal (1–4), mild (5–8), moderate (9–12) and marked (13–18). Out of 103 patients, 7 patients (6.8%) had minimal disease, 67 patients (65%) had mild disease while 29 patients (29%) had moderate disease on liver biopsy. None of them had advanced disease. Similarly liver fibrosis was scored as stage 0 to stage 4. Stage 0 or no fibrosis, was present in 3 (2.9%) patients, mild fibrosis (Stage-1) was seen in 94 (91.3%) patients and stage-3 (severe fibrosis) was present in 6 (5.8%) patients. Stage-4 or cirrhosis was not seen in our patients.

Baseline PCR for HCV RNA showed level of viraemia as low, moderate and high grade. 21 (20.3%) patients had low grade viraemia, 57 (55.3%) patients had moderate grade and 25 (24.3%) patients had high grade viraemia. End Treatment Response (ETR) was achieved in 92 patients (89.3%) with p-value 0.03 (chi-square). There were 75 (81.5%) males and 17 (18.5%) females. There were 11 patients (10.7%) who were non responder, i.e., detectable PCR at the end of 24 weeks of treatment. SVR (sustained viral response) was seen in 89 patients (86.4%) with p value of 0.034 (χ^2-test). There were 89 patients, 72 (80.8%) males and 17 (19.2%) females.

Table-1: Patients' demography and baseline features

Variables		Results
Total No. of patients (n)		103
Males		85 (82.5%)
Females		18 (17.5%)
Mean±SD age (years) (range 21–48)		31.75±5.87
Mean±SD ALT IU/L (range 44–385)		96.17±49.98
HCV RNA/ Viraemia Grade	Low Grade	21 (20.4%)
	Moderate Grade	57 (55.3%)
	High Grade	25 (24.3%)
Biopsy Grading (Inflammation)	Minimal Grade	07 (6.8%)
	Mild Grade	67 (65%)
	Moderate Grade	29 (28.2%)
Biopsy Staging (fibrosis)	No Fibrosis	3 (2.9%)
	Mild Fibrosis	94 (91.3)
	Moderate Fibrosis	06 (5.8%)

ALT=Alanin Amino-Transferase, SD=Standard Deviation

DISCUSSION

HCV is a tremendous health problem not only in Pakistan but also worldwide. Prevalence of hepatitis C is increasing worldwide. Adherence to therapy, decreased viral load, genotype 3, female sex, young age and lower body weight are associated with better viral response to therapy.[12] In all prospective treatment studies, genotype is the strongest predictor of response.[10] In published reports of distribution of different HCV genotypes in Pakistani population, the most predominant HCV genotype is genotype 3 (75–90%), followed by genotypes 1, 2, and 5.[13,14] Peginterferon Alfa (PEG-IFN) and Ribavirin (RBV) for 6–12 months is currently approved initial therapy for patients with chronic HCV infection, which is expensive. But our study was conducted with conventional Interferon Alfa-2b and Ribavirin for 6 months to asses the end of treatment as well as sustained viral response.

In our study, 103 patients after completing 24 weeks of treatment, ETR was 89.3% (p=0.03). Ninety-two (89.3%) patients showed no detectable virus in serum. There were 75 (81.5%) males and 17 (18.5%) females. Our results are not only comparable to but also showed better response when compared with the local results. Agha Babar Hussain *et al*[15] reported ETR of

86.5%, Amina Nadeem[12] 84%, Javed Iqbal Farooqi[16] 86.3% and Sundeep Mukarjee[20] reported a response rate of 90%.

Pegylated interferon, now a days is becoming the interferon of choice in developed countries.[17] However in our setting, standard interferon gives better sustained viral response of more than 80%.[18] Sustained response reported by various local studies, e.g., Ashraf *et al*[19], Sarwar *et al*[14], and Javed Iqbal Farooqi[16] was 79%, 82%, and 85.3% respectively. Sundeep Mukarjee[20] also reported response rate of 80% (Table-2). SVR in our study was primary outcome. It was 86.4% (p=0.034) which was statistical significant. Like ETR, our study also showed better sustained response. This could be due to the fact that our patients were young, and probably due to treatment responsive genotype 3 in our patients.[12]

Table-2: Comparison of our work with others

Study	ETR	SVR
Our Study	89.3%	86.4%
Amina Nadeem[12]	84%	81–86%
Agha Baber Hussain[15]	86.5%	76%
Javed Iqbal Farooqi[16]	86%	81–86%
Sundeep Mukarjee[20]	90%	80%

ETR=End Treatment Response, SVR= Sustained Viral Response

Our study showed that younger patients with early liver disease having mild inflammation and fibrosis on liver biopsy had better response to combination therapy as compared to patients with advanced disease.[10] This observation is supported by Nauman Kashif[21] and Batool[22]. They showed that patients with early liver disease as evidenced by stage 1 and 2 (mild to moderate fibrosis) on liver biopsy had better response to standard Interferon combination therapy as compared to patients with advanced fibrosis (stage 3 and 4).

CONCLUSION

Chronic Hepatitis C patients had better sustained viral response to cheaper standard Interferon and Ribavirin therapy.

REFERENCES

1. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradly DW, Houghton M. Isolation of a cDNA clone derived from a blood borne non-A, non-B viral hepatitis genome. Science 1989;244:359–62.
2. Lo Re V 3rd, Kostman JR. Management of chronic hepatitis C. Postgrad Med J 2005;81:376–82.
3. Ray Kim W. Global epidemiology and burden of hepatitis C. Microbes Infect 2002;4:1219–25.
4. Mahmood MA, Khawar S, Anjum AH, Ahmed SM, Rafiq S, Nazir I, *et al*. Prevalence of hepatitis B, C and HIV infection in blood donors of Multan region. Ann KE Med Coll 2004;10(4):459–61.
5. Hamid S, Umar M, Alam A, Siddiqui A, Qureshi H, Butt J; Pakistan Society of Gastroenterology. PSG consensus statement on management of hepatitis C virus infection- 2003. J Pak Med Assoc 2004;54:146–50.
6. Giannini E, Risso D, Botta F. Validity and clinical utility of the aspartate aminotranferase-alanine aminotranferase ratio in assessing severity and prognosis in patients with chronic hepatitis C virus related chronic liver disease. Arch Intern Med 2003;163:218–24.
7. Sarwar S, Butt AK, Khan AA, Alam A, Ahmad I, Dilshad A, *et al*. Serum alanine aminotranferase level and response to Interferon-Ribavirin combination therapy in patients with Chronic Hepatitis C. J Coll Physicians Surg Pak 2006;16:460–3.
8. Scott JD, Gretch DR. Molecular diagnostics of hepatitis C virus infection: a systematic review. JAMA 2007;297:724–32.
9. Dienstag JL. The role of liver biopsy in chronic hepatitis C. Hepatology 2002;36(suppl 1):152–60.
10. Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. AASLD practice guide lines. Hepatology 2004;39:1147–71.
11. Andriulli A, Mangia A, Iacobellis A, Ippolito A, Leandro G, Zeuzem S. Meta analysis: the outcome of anti-viral therapy in HCV genotype 2 and genotype 3 infected patients with chronic hepatitis. Aliment Ther Pharm 2008;28:397–404.
12. Amina Nadeem, Muhammad Aslam, Dilshad Ahmad Khan, Tassawar Hussain, Saadat Ali Khan. Effects of combined Interferon alpha and Ribavirin therapy on thyroid functions in patients with chronic hepatitis C. J Coll Physicians Surg Pak 2009;19:86–9.
13. Raja NS, Janjua KA. Epidemiology of hepatitis C virus infection in Pakistan. J Microbiol Immunol Infect 2008;41:4–8.
14. Khokhar N, Asif N, Khokhar OS. Serotype 3 is most common hepatitis C serotype in Pakistan: however, significant numbers are untypeable. Hepatology 2003;38:270–1.
15. Agha Baber Hussain, Tassawar Hussain,Masood Anwar,Shujaat Hussain,Yousaf Kazmi, Waheeduz Zaman Tariq, Karamat Ahmed Karamat. Treatment response in HCV related chronic hepatitis. J Coll Physicians Surg Pak 2004;14(8):466–9.
16. Javed Iqbal Farooqi, Rukhsana Javed Farooqi. Efficacy of conventional Interferon alpha 2b plus Ribavirin combination in the treatment of chronic Hepatitis C naive patients. Rawal Med J 2005;30(1):9–11.
17. Hadziyannis HJ, Sette jr, H, Morgan TR, Balan V, Diago M, Marcellin P, *et al*. Peginterferon alfa 2-a and ribavirin combination therapy in chronic hepatitis C. Ann Intern Med 2004;140:346–55
18. Khokhar N, Hepatitis C: Are we getting close to control? Rawal Med J 2005;30(1):1. (Editorial)
19. Ashraf M, Asghar M, Khan MN, Batool A, Asad J. Chronic Hepatitis C; effect of Ribavirin therapy on liver functions Professional Med J 2001;8:487–90.
20. Mukherjee S, Katz J, Dhawan VK, Wu GY, Talavera F, Brann OS, *et al*. Hepatitis C. Available at: www.eMedicine.Medscape.com Accessed June 25, 2010.
21. Kashif N, Saeed S, Ahmad TM. Relationship between fibrosis score and response to interferon alfa and ribavirin combination therapy in chronic HCV infection. Pak Aremd Forces Med J 2009;59(1):43–7.
22. Batool Q, Qureshi S. Declining sustained virological response in Hepatitis C. J Coll Physicians Surg Pak 2006:16;187–91.

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