Original Article

Higher Response Rate of Patients with Chronic Hepatitis C to Combination of Conventional Interferon and Ribavirin

*Rehman-ud-din **
*Ihsanullah Mahsud***
*Musharaf Ali Khan****
*Nasim Saba*****

** Assistant Professor and Gastroenterologist*
Department of Medicine
Gomal Medical College
Dera Ismail Khan
***Associate Professor and Head*
Gomal Medical College
Dera Ismail Khan
****Assistant Professor Urology*
PIMS, Islamabad.
*****Assistant Professor and Head*
Department of Gynaecology & Obstetrics
Gomal Medical College
Dera Ismail Khan

Address for Correspondence:
*Dr. Ishanullah Mahsud**
Associate professor Department of Gynaecology & Obstetrics and Head
Gomal Medical College
Dera Ismail Khan

Background: Hepatitis C virus infection is a common problem world-wide In developed countries pegylated interferon is used for treatment of hepatitis C and has been shown to be superior to conventional interferon. However, pegylated interferon is very costly and is beyond the reach of majority of the patients in our country.

Objective: To look into the response of patients with chronic hepatitis C to treatment with conventional interferon given in combination with ribavirin.

Materials and Methods: The study was conducted at Dera Ismail Khan from April 2004 to April 2008, involving patients attending either medical OPD of District Headquarter Teaching Hospital or consulting physicians of this hospital at their private clinics. Two hundred and fifty adult patients, both male and female, eligible for therapy were studied after informed consent. Interferon alfa 2b was given in a dose of 3 million units subcutaneously thrice a week alongwith ribavirin 800 to 1200 mg daily in divided doses for a period of 24 weeks. Patients were tested for absence of detectable HCV RNA by PCR at the end of treatment (end of treatment response) and 24 weeks after completion of therapy (sustained virological response).

Results: In this study, 84% patients showed end of treatment response and 72.8% manifested a sustained virological response. There was no significant difference between the two sexes in their response to treatment..

Conclusion: The response rate of patients with chronic hepatitis C to conventional interferon and ribavirin combination is high in our area compared to many studies conducted in other parts of the world.

Key words: Hepatitis C virus, interferon, ribavirin.

Introduction

Hepatitis C virus (HCV) infection has a worldwide distribution with a prevalence of about 3%. About 15% of the patients make spontaneous recovery while the remaining 85% remain chronically infected.[1] Chronic HCV infection affects an estimated 170 million people throughout the world.[2] Almost 20% of these patients develop hepatic cirrhosis within about 20 years. Six percent develop terminal hepatic disease and 4% end with hepatocellular carcinoma (HCC).[3-5] HCV is transmitted by parenteral or permucosal exposure to infected blood or body fluids.[2] Sexual transmission of HCV between monogamous partners is rare[6] and many authorities do not advise the use of barrier precautions such as condoms in these cases. HCV is not transmitted by hugging and the sharing of eating utensils. HCV transmission at the time of delivery is 1 to 5%. Acupuncture, body piercing, tattooing and commercial barbering are also considered to be involved in transmission of HCV infection. There is little evidence that HCV is transmitted by breast milk. Therefore, HCV infected mothers should not avoid breast feeding.[7]Patients with chronic HCV infection are often asymptomatic[2] or may present with non specific symptoms of aches and pains and a feeling of being unwell. Jaundice is rarely observed in these patients.[8] In contrast to hepatitis B, recovery from hepatitis C does not mean life-long immunity to HCV. Multiple episodes of acute hepatitis have been reported in thalassemic children receiving repeated blood transfusions[9]. In patients that recover from HCV there is a decline and eventual loss of HCV specific antibodies after 10 to 20 years.[10]

There are six genotypes of HCV[11]. The genotype most prevalent in Pakistan is type 3, which has a favourable response to interferon.[12-14] The purpose of this study was to know about the response of patients with chronic HCV infection to conventional

interferon and ribavirin combination therapy in our area where HCV infection is an important cause of morbidity and mortality but where no such study has been conducted in the past.

This study was conducted to look into the response of patients with chronic hepatitis C to treatment with conventional interferon given in combination with ribavirin.

Materials and Methods

The study was conducted in Dera Ismail Khan during a period of four years from April 2004 to April 2008. The study was started with 260 patients but 6 patients lost follow up and were excluded from the study. Four more patients could not continue the treatment because of side effects of the drugs. One of these develop severe psychiatric symptoms and the other 3 became anaemic with Hb of less than 9gm/dl. The remaining 250 patient were thus finally included in the study.

The patients belonged to district Dera Ismail Khan, District Tank, North and South Waziristan Agencies, District Zhob (Baluchistan) and from areas of Afghanistan adjacent to Pak-Afghan border. These patients either attended medial O.P.D of District Headquarter Teaching Hospital D.I.Khan or private clinics of physicians working in this hospital.

All adult patients, both male and female, with chronic HCV infection and eligible for therapy were included in the study after informing them about the study and obtaining their consent. In cases of acute onset treatment was delayed for three months to allow for spontaneous clearance of the virus. However, in general medical practice majority of the patients already have chronic hepatitis C.

Exclusion criteria were:

- Those having received interferon and ribavirin therapy in the past.
- Patients with decompensated cirrhosis or hepatocellular carcinoma.
- Pregnant ladies or those unable to comply with barrier contraception.
- Poorly controlled major depressive illness.
- Uncontrolled hyperthyroidism.
- Chronic renal insufficiency.
- Poorly controlled diabetes mellitus.
- Hemoglobin disorders.
- Significant co-morbidity e.g. severe cardiac or pulmonary disease.
- Active or suspected malignancy.
- Renal, cardiac or other solid organ transplant patients.
- Autoimmune hepatitis.
- Known hypersensitivity to either interferon or ribavirin.

ELISA was used for detection of antibodies to HCV (Anti-HCV). Confirmation of infection was done by detection of HCV Ribonucleic Acid (RNA) by qualitative polymerase chain reaction (PCR) because quantitative HCV RNA tests are not only expensive but also less sensitive than qualitative tests.[15,16] Liver biopsy was not done routinely because of the potential risk of the procedure, concern of sampling error[17] and the fact that patients infected with HCV genotype 2 and 3 have a high likelihood of response to interferon and may be treated without resorting to liver biopsy[7]. The patients were treated irrespective of Alanine Aminotranfarase (ALT) levels as it has been shows that 14 to 24% of persons may have progressive liver disease over time despite presence of normal ALT values.[18,19] Other studies have also shown clinically and histologically advancing liver disease despite persistently normal ALT values[20].

The patients were given conventional interferon alfa 2a in a dose of 3 million units subcutaneously thrice a week alongwith ribavirin 800 to 1200 milligram daily, according to body weight, in divided doses for a period of 24 weeks. Hemoglobin (Hb), total leukocyte count (TLC), differential leukocyte count (DLC), platelet count and ALT levels were checked in the beginning of the study, and at monthly intervals throughout the treatment. Those developing severe neutropenia, thrombocytopenia or anaemia were excluded from the study. Flu like symptoms were managed with antipyretics and non-steroidal anti-inflammatory drugs (NSAIDs). Anti-depressant such as SSRIs were given to patients remaining symptomatic despite explanation and reassurance. Those having severe depression despite all these measures were excluded from the study.

HCV RNA was checked initially for confirmation of diagnosis and then after completion of therapy and 24 weeks after completion of therapy. Because of problem of cost and difficulties in transportation of samples to laboratories situated at Lahore, Islamabad and Karachi, either through Prime Minister Programme or via referral centers of private laboratories, patients were not tested for early virological response. Absence of detectable HCV RNA at the end of treatment i.e. end of treatment response (ETR) and absence of detectable HCV RNA 24 weeks after completion of therapy i.e. sustained virological response (SVR) were determined. Patients showing no ETR were labeled non-responders and those having ETR but no SVR as relapsers. Comparison was made with other studies. Non-responders and relapsers, having sufficient resources, were advised about genotyping and viral load determination so as to be treated by pegylated interferon and ribavirin combination.

Results

Out of the 250 patients that could be followed

throughout the study 148 (59.2%) were male and 102 (40.8%) were female. Age range was from 20 to 59 years mean age being 36.73 years. One hundred and seventy two (68.8%) patients were < 40 years of age. Only 30 (12%) patients were > 50 years of age. Out of the 250 patients HCV RNA was undetectable in 210 (84%) patients at the end of treatment and remained undetectable in 182 (72.8%) patients after completion of therapy. Among 148 male patients ETR was in 128 (86.5%) and SVR in 106 (71.6%) patients. Out of 102 female patients 82 (80.4%) patients were having ETR and 76 (74.5%) were having SVR.

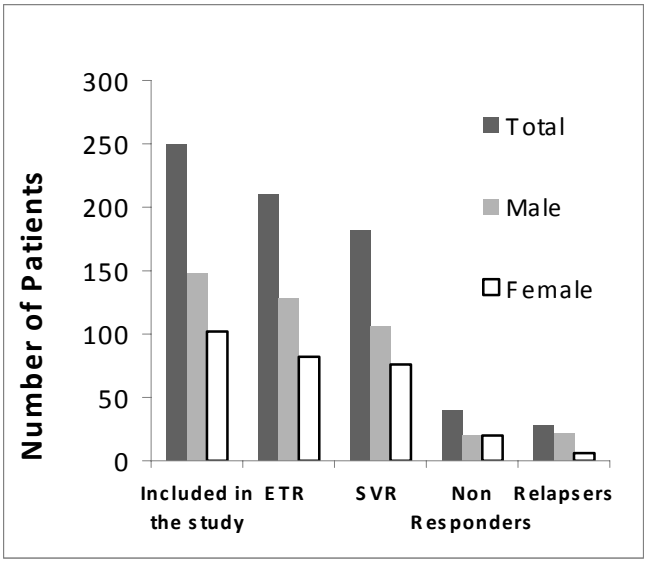

Figure 1 Number of Patients and Their Response to Treatment (n=250)

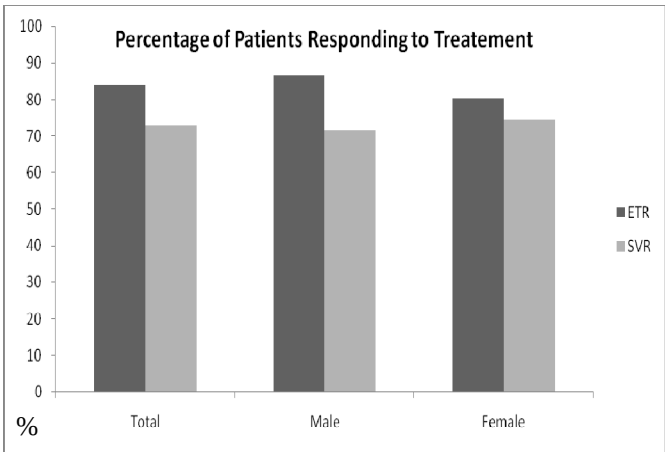

Figure 2: Percentage of Patients Responding to Treatment(n=250)

Discussion

In HCV infection the goal of treatment is to prevent complications of infection by eradication of infection. Infection in considered eradicated when there is SVR defined as the absence of HCV RNA in the serum by a sensitive test at the end of treatment and six months after completion of therapy. However a small proportion of patients who achieve SVR may develop HCC even without passing through a stage of cirrhosis. Therefore long term follow up of the patients with SVR is mandatory and should include surveillance for HCC.[21] Thus it is unclear whether the virus is truly eradicated as some studies have shown that the virus may remain in the body at low levels after successful treatment. However French researchers conducted a long term follow up study and noted that residual RNA was observed only in liver tissue in 1.7% of patients and concluded that SVR may be considered to show eradication of HCV infection.[22]

The very high ETR and SVR in this study may be because of the fact that in Pakistan the most common genotype is 3 which is highly responsive to standard interferon.[23] The ETR and SVR in this study is high compared to the study conducted by Zuberi et al showing SVR and ETR rates of 70% and 33% respectively.[24] However only 74 patients were included in their study and patients treated in their study were of higher age group compared to those in our study. Higher SVR rates in patients less than 40 years of age have been reported by other authors as well.[25] In our study 172 (68.8%) patients were not more than 40 years of age. A recent study by Yu et al.[26] with pegylated interferon (PgIF) has reported 94% SVR. Higher SVR rates of 76-82% using peg interferon have been reported by other research workers as well.[2,7] Although genotyping was advised to non-responders and relapsers, the patients did not get these tests done because of financial constraints. It is of interest that lately significant increase in relapsers has been observed in genotype 3 in Pakistan

In this study patients were treated irrespective of serum ALT level because of the possibility of severe histological changes despite normal ALT levels.[18,19] Liver biopsy was not essential because the genotype prevalence in Pakistan is type3 having better response to therapy and may be treated without subjecting the patient to liver biopsy[7]. Some authorities are of the opinion that patients with persistently normal ALTs and mild disease at baseline tend to have slower disease progression and such patients may need only close monitoring[2]. In an area like D.I.Khan such a monitoring is very difficult because of various factors. Serodiagnostic and other markers of fibrosis are in development and trials are in progress to know about their clinical utility in replacing liver biopsy in HCV infected patients.[28]

Conclusion

The response rate of patients with chronic hepatitis C to conventional interferon and ribavirin combination is high in our area compared to many studies conducted in other parts of the world and the results obtained with this regimen are as good as those achieved with PgIF and ribavirin combination in other studies. Studies are needed with PgIF and ribavirin combination in this part of the world so as to compare the results with those obtained in our study.

References

1. Wasley A, Alter M.J, Epidemiology of hepatitis C: geographic differences and temporal trends. Semin liver dis 2000; 20(1): 1-16
2. Patel K, Muir AJ, McHutchison JG. Diagnosis and treatment of chronic hepatitis C lifection BMJ 2006; 332: 1013-1017.
3. Serfaty L, Aumaitre H, Chauzouilleres. Determinants of outcome of compensated hepatitis C virus-related cirrhosis. Hepatology 1998; 27: 1435-1440.
4. Di Bisceglie A.M. natural history of hepatitis C: its impact on clinical management. Hepatology 2000; 31(4): 1014-1018.
5. Alter H.J, seeff LB. recovery, persistence, and sequlae in hepatitis C virus infection: A persfective on long-term outcome. Semin Liver Dis 2000; 20(1): 17-35.
6. Alter M.J. prevention of spread of hepatitis C. hepatology 2002; 36 (Suppl: 1): 593-598.
7. Strader DB, Wright T, Thomas DL and Seeff LB, Diagnosis management and treatment of hepatitis C. Hepatology 2004; 39: 1147-1171.
8. Rehermann B, Nascimbeni M. Immunulogy of hepatitis B virus and hepatitis C virus infection. Nature reviews. Immunology 2005; 5; 215-229.
9. Lai M, et al. Hepatitis C virus in multiple episodes of acute hepatitis in polytransfused thalasaemic children. Lancet 1994; 343: 388-390.
10. Takaki A et al. Cellular immune responses persist, humoral immune responses decsease two decades after recovery from single source outbreak of hepatitis C. Nature Med 2000; 6: 578-582.
11. Simmonds P. Viral hetrogenicity of the hepatitis C virus. J Hepatol 1999; 31 (Suppl): 54-60.
12. Ahmad N, Asghar M, Shafique M, Qureshi JA. An evidence of high prevalence of hepatitis C virus in Faisalabad Pakistan. Saudi Med J 2007; 28: 390-395.
13. Moatter T, Hussainy AS, Hamid S, Ahmad Z, Siddqui S. Comparative analysis of viral titers and histologic features of Pakistani patients infected with hepatitis C virus type 3. Int J. Infect Dis 2002, 6: 272-276.
14. Ahmad M, Bukhari A, Ghanni MHU, Khan A, Malik JI, Shah AH. Prevalence of hepatitis C virus and its serotypes in Bahawalpur division. Biomedical 2003; 19: 18-22.
15. Pawlotsky JM. Use and interpretation of virological test for hepatitis C. Hepatology 2002; 36 (Suppl 1)S65-S73.
16. Pawlotsky JM, Lonjon I, Hezode C, Raynard B, Darthuy F, Remire J, et al. What strategy should be used for diagnosis of hepatitis C virus infection in clinical laboratories. Hepatology 1998; 27: 1700-1702.
17. Regev A, Berho M, Jeffers L.J, Milikowski C, Molina EG, Pyrsopoulos NT et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic hepatitis C virus infection. Am J Gastroenterol 2002; 97: 2614-2618.
18. Pradot P, Alberti A, Poynard T, Esteban JI Weiland O, Marcellin P et al. Predictive value of ALT levels for histologic findings in chronic hepatitis C: A European collaborative study. Hepatology 2002 36: 973-977.
19. Hui CK, Belaye T, Montegrande K, Wright TL. A comparison in the progression of liver fibrosis in chronic hepatitis C between persistently normal and elevated transaminases. Hepatol 2003; 38: 511-517.
20. Persico M, Persico E, suozzo R, Conte S, De Seta M, Coppola L et al. Natural history of hepatitis C virus carriers with persistently normal aminotransferase level. Gastroentology 2000; 118: 760-764.
21. Scherzer TM, Reddy KR, Wibra F. hepatocelluler carcinoma in long-term sustained virological responders following antiviral combination therapy for chronic hepatitis C. J Viral hepatitis 2008; 15: 659-665.
22. Maylin S, Martinot-Peignoux M, Moucari R. Eradication of hepatitis C virus in patients successfully treated for chronic hepatitis C. Gastroentology 2008; 135: 821-829.
23. Ahmad SI, Mahmud MR, Khan NY, Naseemullah M, Hanif M. Pegylated interferon and ribavirin in HCV genotype 3 detectable patients after 12 weeks of conventional interferon-ribavirin treatment. Pakistan J Gastroenterol 2006; 20: 58-62.
24. Zuberi BF, Zuberi FF, Memon SA, Qureshi MH, Ali SZ, Afser S. sustained virological response based on rapid virological response in genotype 3 chronic hepatitis C treated with standard interferon in the Pakistani population. World J gastroenterol 2008; 14(4): 2218-2221.
25. Fried MW, Shiffman MI, Reddy KR, Smith C, Marinos G, Goncales FL, Jr et al. Peginterferon alfa 2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002; 347: 975-982.
26. Yu MI, Dai CY, Huang JF, Hou NJ, Lee LP, Hsieh MY et al. A randomized study of piginterferon and ribavirin for 16 versus 24 weeks in patients with genotype 2 chronic hepatitis C. Gut 2007; 56: 553-559.
27. Afdhal NH, Nunes D. Evaluation of liver fibrosis: a concise review. Am J Gastroenterol 2004; 99: 1160-1174.
28. Rocky DC, Bissel DM. Non-invasive measures of liver fibrosis. Hepatology 2006; 43(suppl 1): S113-S120.