ORIGINAL ARTICLE

COMPARISON OF POLYMERASE CHAIN REACTION BEFORE AND AFTER INTERFERON ALPHA AND RIBAVIRIN COMBINATION THERAPY IN CHRONIC HEPATITIS C INFECTION

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ABSTRACT

Background: Hepatitis C virus infects an estimated 170 million persons worldwide. Combination therapy has been approved for treatment of patients with chronic hepatitis C. The response rates are variable depending upon the genotype of hepatitis C virus. This study was designed to determine the therapeutic significance of interferon alpha and ribavirin combination therapy in patients with Chronic Hepatitis C Virus infection in our set up.

Material &Methods: The study was carried out at Military Hospital Rawalpindi, from January 2005 to December 2005. A total of 60 adult patients both male and female were included in the study on the basis of the presence of anti-HCV antibodies, elevated serum ALT, a positive PCR for HCV RNA and compensated liver disease on liver biopsy. All patients were treated with interferon alpha and ribavirin. This treatment was given for six months. All the patients were evaluated for end treatment response at six months of therapy.

Results: Forty-four (73.3%) patients showed response to six months of combination therapy ($p<0.05$) and were labeled as responders (having PCR for HCV RNA negative). Non-responders (PCR for HCV RNA positive) were 16(26.7%). Out of the 51 males in the study, there were 37(72.5%) responders while 14(27.5%) were non-responders. Out of 9 females, 7(77.8%) were responders while 2(22.2%) were non-responders.

Conclusion: The response to six months of interferon alpha and ribavirin combination therapy was 73% in my study, which is therapeutically important.

Key Words: Hepatitis C virus, Polymerase chain reaction, interferon alpha.

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INTRODUCTION

Hepatitis C virus (HCV) infects an estimated 170 million persons worldwide and thus represents a viral pandemic.[1]It became apparent after the discovery of the hepatitis A and B viruses in the late 1960s and early 1970s that a large proportion of cases of acute and chronic hepatitis could not be explained by either of these agents. Another viral agent was suspected, and patients infected with this suspected agent were said to have non-A, non-B hepatitis. The agent was finally identified in 1989 when the genome of the virus was cloned and the agent was designated the hepatitis C virus (HCV).[2]

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Infection with the hepatitis C virus can result in both acute and chronic hepatitis. Sixty to eighty percent of cases develop chronic hepatitis, cirrhosis occurs in up to 50 percent of chronically infected patients, and about fifteen percent will finally develop hepatocellular carcinoma.[3-5]

Prevalence of HCV is highest in Egypt while lowest in Scandinavians countries (>0.5%). In Pakistan the incidence varies between 3% and 7% depending on the area.[6-7]

After a decade the next major step in treatment of chronic hepatitis C emerged, namely, the combination of interferon alpha with the oral nucleoside analogue ribavirin. Although ribavirin alone does not seem to be active against the hepatitis C virus, the combination resulted in improved and sustained biochemical, virological and histological response rates.[8-10]

My study will only review combination of interferon alpha with ribavirin. Combination therapy has been approved for treatment of patients with chronic hepatitis C who have compensated liver disease previously untreated with alpha interferon or who have relapsed following interferon monotherapy.

The population in Pakistan is having problem at larger scale as compared to western world.[11-13] My study will determine the end treatment response after six months of combination therapy in our population.

MATERIAL AND METHODS

This Quasi-experimental study was carried out at Military Hospital Rawalpindi which is a tertiary care center and a 1000 bed military hospital treating the military and local civilian population. The study was of one year duration and carried out from January to December 2005. A total of 60 patients were included in the study. All the patients were allotted a serial number, which was indicated on all their documents and investigations. Non-probability convenience sampling was used as a sampling technique.

Adult patients of all ages both male and female with chronic HCV infection were included in the study who were Anti-HCV positive, had elevated Serum ALT, PCR for HCV RNA positive and compensated liver disease on liver biopsy.

The patients who were already treated with interferon therapy, were simultaneously infected with hepatitis B virus, had cirrhosis liver, had other chronic illnesses like renal failure, anemia, cardiac failure and malignancy or in whom anti-viral therapy will be discontinued due to any reason were excluded from the study.

Name, age, sex, address, weight and occupation of all the patients were noted on the study proforma for all the patients. The presenting symptoms along with relevant investigations were also noted. Clinical examination was performed to rule out other diseases. All patients were treated for 6 months with interferon alpha, 3 million units thrice a week s/c and ribavirin 1200 mg/day orally for patients weighing more than 75 kg and 1000 mg/day for patients weighing less than 75 kg. For the laboratory investigations, Armed Forces Institute of Pathology Rawalpindi and Pathology Department of Army Medical College were used. The investigations done before start of treatment were hemoglobin, TLC, DLC, platelet count, serum bilirubin, ALT, alkaline phosphatase, USG abdomen, prothrombin time, anti-HCV antibodies, HCV-RNA by PCR, HBsAg and liver biopsy.

Liver biopsy was done in the hospital under strict aseptic conditions, before start of treatment using surecut needle, to assess the histopathological condition of the liver. Knodell score was recorded for all patients on histopathological examination of liver biopsy sample.

After six months of combination therapy, PCR for HCV-RNA was repeated. For PCR, the sera were separated and kept at -20^{0}C and tested within three days of collection of samples.

All the patients were evaluated for end treatment response (ETR) at the end of 6 months of interferon alpha and ribavirin combination therapy. Responders were taken as having PCR for HCV-RNA negative.

Statistical package for social sciences (SPSS) version 10.0 was used to analyze the data. Frequency and percentages were computed for categorical variables like sex and response rate after 6 months of combination therapy. Mean and standard deviation was computed for quantitative variables like age. Histogram was presented for normal distribution of age. Chi-square test was applied to compare proportion of difference between gender and age groups with PCR for HCV-RNA. $P < 0.05$ was considered as significant.

RESULTS

Among 60 patients; 51 were males and 9 females. The age range of patients was 20 to 44 with mean age of 30.7+6.58 years. They were divided into five age groups. (Fig. 1)

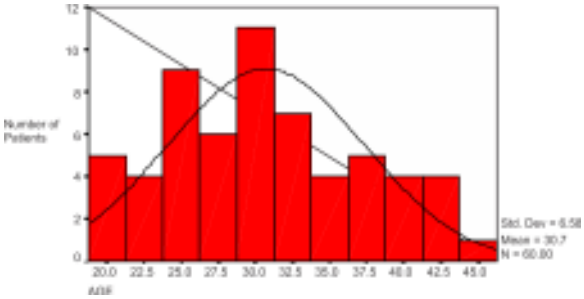

Fig. 1: Histogram of age.

The patients included in the study were tested for ETR after 6 months of combination therapy. Forty-four (73.3%) had PCR for HCV-RNA negative and were responders, while the rest 16 (26.7%) had PCR for HCV RNA positive and were non-responders ($p = 0.01$).

Highest response rate was seen in the age group 40-44 years which was 100% while lowest response rate was seen in the age group 35-39 years which was 60%. (Table 1)

Table 1: Response rate in different age groups after six months of combination therapy.

Age groups	PCR for HCV-RNA		Total
	Negativen n(%)	Positiven n(%)	
20-24	9 (81.8%)	2 (18.2%)	11
25-29	12 (66.7%)	6 (33.3%)	18
30-34	10 (71.4%)	4 (28.6%)	14
35-39	6 (60.0%)	4 (40%)	10
40-44	7 (100%)	0	7
Total	44 (73.3%)	16 (26.7%)	60

PCR=Polymerase chain reaction; HCV=Hepatitis C virus; RNA=Ribonucleic acid

DISCUSSION

Hepatitis C virus today involves a large portion of world population. The active virus infection is only determined if the viral RNA is detected.[15] Combination therapy with interferon alpha and ribavirin is the recommended treatment for patients with HCV related chronic liver disease. Interferon alpha decreases mRNA and proteins necessary for viral replication whereas Ribavirin inhibits RNA dependent RNA polymerase in HCV infected cells, thus decreasing guanine tri-phosphate (GTP) availability for viral replication. A synergistic response is seen when Ribavirin and interferon alpha are given in combination.[16] Monitoring of the patients for HCV RNA viremia after treatment is essential to see end-of-treatment response. Although initial assessment of viral load may be a good predictor of the possible outcome of the treatment, the monitoring of response to the treatment is recommended with qualitative HCV-RNA assays.[17] PCR is an important tool for detection of HCV-RNA in hepatitis C virus infection in our setup.[10]

Out of 60 patients tested for ETR in my study, 73.3% had negative PCR for HCV RNA and were responders, while the rest 26.7% had PCR for HCV RNA positive and were non-responders. This 73.3% response rate in our study is comparable to 71.4%, 73% and 72.4% observed by others.[10,18,19] Hussein et al observed a higher response rate of 86.5%.[20] The response rate of 31 to 38 per**c**ent was observed by M**c** Hut**c**hison et al[8] and Davis et al[14] when they initially used the combination therapy. But when the individual genotypes were observed, the response rate was different in different genotypes. The response rate was 17% with the genotype 1 and 62% with the genotype 2 and 3.[8-9]

The better response rate observed in our patients from other studies carried out in Pakistan is due to the presence of the genotype 3 found in the majority of our cases. End-of-treatment response was slightly better in females (77.7%) as compared to males (72.5%).

CONCLUSION

My study concludes that end-of-treatment response to six months of interferon alpha and ribavirin combination therapy in chronic hepatitis C is 73.3%, which is therapeutically important.

REFERENCES

1. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med 2001;345:41-52.
2. Choo QL, Kuo G, Weiner AJ. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 1989;244:359-62.
3. Alter MJ, Mast EE. The epidemiology of viral hepatitis in the United States. Gastroenterol Clin North Am 1994;23:437-55.
4. Tong MJ, El-Farra NS, Reikes AR, Co RL. Clinical outcomes after transfusion-associated hepatitis C. N Engl J Med 1995;332:1463-6.
5. Tilg H. New insights into the mechanisms of interferon alpha: an immunoregulatory and anti-inflammatory cytokine. Gastroenterology 1997;112:1017-21.
6. Zuberi SJ. Seroepidemiology of HBV/HCV in Pakistan: Int Hepatol Communication 1996;5:19-26.
7. Farid S, Mohammad S, Iftikhar AM, Iftikhar H. Increasing prevalence of chronic hepatitis and associated risk factors. Pak J Med Res 2002;41:46-50.
8. McHutchison JG, Gordon S, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, et al. Interferon alfa-2b monotherapy versus interferon alfa-2b plus ribavirin as initial treatment for chronic hepatitis C: results of a US multicenter randomized controlled study. N Engl J Med 1998;339:1485-92.
9. Poynard T, Marcellin P, Lee S, Niederau C, Minuk GS, Ideo G, et al. Randomized trial of interferon alpha-2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha-2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. Lancet 1998;352:1426-32.
10. Hussein A, Tariq W, Karamat K, Ghani E, Mushtaq S, Hussein T. HCV viremia in clinical and biochemical perspective. J Coll Physicians Surg Pak 2000;10:409-11.
11. Muhammad AN, Tariq W, Abdul MS, Nasrullah G, Khadija I, Syed SH. Hepatitis C virus: an alarmingly increasing cause of liver cirrhosis in Pakistan. Pak J Gastroenterol 2002;16:3-8.

12. Mehmood A, Karamat KA, Mubarik A, Rehman ZU. Prevalence of hepatitis C virus antibodies in cases of chronic hepatitis and cirrhosis at PNS Shifa, Karachi. Pak Armed Forces Med J 1999;49:15-7.

13. Khokhar N. Management of chronic hepatitis C. J Rawal Med Coll 2001;5:104-6.

14. Frank C, Mohamed MK, Strickland GT, Lavanchy D, Arthur RR, Magder LS, et al. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. Lancet 2000;355:887-91.

15. Enomoto M, Nishiguchi S, Shiomi S, Takeda M, Fukuda K, Ueda T, et al. Comparison of real time quantitative polymerase chain reaction with three other assays for quantitation of hepatitis C virus. J Gastroenterol Hepatol 2001;16:904-9.

16. Gutfreund KS, Bain VG. Chronic viral hepatitis C: management update. CMAJ 2000; 162:827-33.

17. Nakamuta M, Fukotomi T, Shimohashi N, Kinukawa N, Uchimura K, Tada S, et al. Kinetics of hepatitis C virus during interferon therapy as a marker of therapeutic response. J Gastroenterol Hepatol 2001;16:29-33.

18. Sheikh WM, Sheikh MA, Solangi GA, Zuberi BF. Role of Interferon and Interferon plus ribavirin in the management of chronic hepatitis C. J Coll Physicians Surg Pak 2002;12:609-12.

19. Hussein AB, Karamat KA, Khan MN, Tariq WZ, Rehman Z, Hussein T. Molecular response to treatment in HCV infected patients. Pak J Pathol 2001;12:8-10.

20. Hussein AB, Hussein T, Anwar M, Hussein S, Kazmi Y, Tariq WZ, et al. Treatment response in HCV related chronic hepatitis. J Coll Physicians Surg Pak 2004;14:466-9.

CONFLICT OF INTEREST
Authors declare no conflict of interest.
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None declared.