TREATMENT RESPONSE OF HEPATITIS C PATIENTS TO COMBINATION THERAPY OF INTERFERON PLUS RIBAVIRIN

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ABSTRACT

Objective: To evaluate effectiveness and safety of 24 weeks combination treatment with Interferon and Ribavirin as initial therapy of chronic hepatitis C patients.

Material and Methods: This study was conducted in Medical unit DHQ Hospital Daggar District Buner from January 1999 to June 2002. Three hundreds and fifty consecutive non cirrhotic, chronic hepatitis C patients (Male=176 Female=174) with positive HCV anti bodies by 3rd generation ELISA, positive HCV RNA by polymerase chain reaction (PCR) and raised serum amino transferase (ALT) were prospectively evaluated and treated with combination of interferon alfa 2-b three million units subcutaneously three injection weekly and ribavirin 800-1200 mg orally daily for 24 weeks and followed for another 6 months. The HCV RNA was checked after 12 weeks and then at the end of the treatment. The ALT level was checked after 04 weeks, then at 12 weeks, and at the end of the treatment. End of the treatment viral response, sustained viral response and side effects of therapy were noted.

Results: Normal ALT was observed in 260 (74.2%) of the patients after 01 month of treatment and 310 (88.5%) of the patients at the end of 03 months. HCR RNA was not detectable in 275 (78.5%) of the patients at the end of 03 months (12 weeks of treatment). At the end of 24 weeks of treatment the HCV RNA was not detectable in 298 (85.14%) patients. Two hundred and seventy six (78.85%) of the patients had persistently normal ALT and HCV RNA in the six months follow up after treatment.

Conclusion: 1) Combination treatment of interferon plus ribavirin for 24 weeks is effective in terms of biochemical and virological response. 2) The side effects are quite tolerable and managable.

Key words: Chronic hepatitis C, interferon, ribavirin, virological response.

INTRODUCTION

Chronic hepatitis C infection is now recognized as an important health care problem[1]. It is the commonest cause of liver cirrhosis and hepatocellular carcinoma (HCC).[2,3] Nearly 4 million Americans are infected and cirrhosis will eventually develop in at least 15-20 % of them[4]. It is also the most common cause of chronic liver disease in Europe, Australia and is the strong reason for liver transplantation in western countries[5].

Interferon was first evaluated in chronic hepatitis C in 1986 [6]. A common regimen of 3 million units of interferon alpha thrice weekly for 24 weeks can normalize serum alanine amino transferase (ALT) levels in 40%-50% of the patients during treatment [7,8]. Nevertheless, the rate of sustained ALT response is usually <25%. Serum hepatitis C virus (HCV) RNA may still be positive in upto 40% of patients with sustained ALT normalization after interferon therapy and late relapse may occur [9,10].

Few studies have suggested the superiority of 48 weeks treatment on 24 weeks, though patients may still relapse.[4,6,11,12] optimal treatments to induce long term biochemical and virological remission in patients with chronic hepatitis C remains a great challenge. Ribavirin (nucleoside analogue) can decrease serum ALT levels temporarily in patients with chronic hepa-titis C but clearance of HCV RNA does not occur[13,14,15].

A combination of interferon and ribavirin is the current treatment and achieves a better response than interferon or ribavirin alone[15,16,17]. The goals of therapy are to slow disease progression, reduce infectivity and decrease the risk of hepatocellular carcinoma. Therefore this prospective study was designed to evaluate the efficacy of interferon plus ribavirin in the management of chronic hepatitis C.

MATERIAL AND METHODS

This prospective study was conducted in the medical unit of DHQ Hospital Daggar from January 1999 to June 2002. A total of 350 non cirrhotic, chronic hepatitis C patients (M-176, F-174), aged between 20-60 years (mean 39.5 $\pm$ 10) who presented with non specific symptoms of dyspepsia, heart burn, bloating, generalized body aches and pain right hypochondria with persistently raised ALT above normal for at least six months, positive HCV antibodies by 3rd generation Elisa, Positive HCV RNA PCR, normal size of the portal vein, i.e. less then 13mm in diameter, normal echo texture of the liver parenchyma by ultrasound were included in the study. None of the patient had liver biopsy, HCV quantification and genotype.

The exclusion criteria was, those who were below 20 years and above 60 years of age, those with other causes of chronic liver disease (Chronic Hepatitis B, Wilson's disease, haemochromatosis), those who were pregnant, those with total leucocytes counts less then 2500/mm^3, those whose haemoglobin were less then 10 gram/dl, those with other serious medical illness were excluded from the study. Before starting the treatment, each patient was counselled about the nature of the disease, cost of treatment, response to treatment and the possible side effects. All the patients were given injection interferon 3MIU subcutaneously thrice weekly plus capsule ribavirin orally according to the body weight (those less then 50kg, 800mg/day, 50 to 75Kg, 1000mg/day, and those more then 75Kg, 1200 mg/day) for six months.

At the start of the treatment the biochemical and haematological status of the patients was assessed which include haemoglobin concentration, total and differential leukocyte counts and platelet count. The biochemical tests performed was blood

sugar, serum creatinine and serum uric acid. During the subsequent visits at week 1, 4, 8, 12, 16, 20 and 24, the haemoglobin concentration, total and differential leucocytes count, platelet counts and ALT was performed for every patient. The other investigations including thyroid function tests (TFTs) were performed when clinically indicated. Efficacy of anti-viral therapy was assessed with normalization of ALT and absence of serum HCV RNA measured at week 12 and being undetectable at the end of the treatment at 24 weeks which constituted end of treatment response and at the end of follow up (6 months after end of treatment) which constituted the sustained viral response.

RESULTS

Three hundred and fifty non-cirrhotic patients, 176 were males and 174 females, having ages between 20 to 60 years (Mean 39.5 ± 10) as shown in table 1 were included in the study.

Fifteen patients discontinued treatment due to severe side effects of interferon. One hundred and seventy males and one hundred and sixty five females, making a total of three hundred and thirty five patients completed the treatment.

DEMOGRAPHIC OF PATIENTS TREATED (N=350)

Age	Male	Female	Total
20-30	25	22	47
31-40	40	75	115
41-50	75	50	125
51-60	36	27	63
Grand Total	176	174	350

TABLE–1

Before treatment the levels of ALT were ranged from 65 to 250 (mean 105 ± 10) as shown in Table 2.

ALT DISTRIBUTION IN HCV POSITIVE PATIENTS

Level of ALT	No. of Patients n=350
65 to 85	125(35.71%)
86 to 150	150 (42.85%)
151 to 200	45 (12.85%)
201 to 250	30(8.57%)

TABLE–2

The ALT returned to normal in 260 patients at the end of four weeks of treatment and 310 at the end of twelve weeks. HCV RNA was done at 12 weeks and then at the end of treatment. The response rate at 12 weeks was 78.5% (275 patients) and at the end of 24 weeks was 85.14% (298 patients) (Table 3).

FALL OF HCV RNA PCR

Weeks of treatment	No. of patients with negative PCR	Percentage
12 weeks	275	78.5%
24 weeks	298	85.14%

TABLE–3

The treatment was well tolerated by all patients except 15 patients who discontinued treatment.

The side effects were mostly influenza-like which occurred in almost all patients. Gastrointestinal, psychiatric, dermatological symptoms and other side effects were tolerable and they are shown in Table-4.

DISCUSSION

The currently approved initial therapy for patients with chronic hepatitis C infection is combination of interferon plus ribavirin for 6 months. The response rate to previously used monotherapy of interferon alone for 6 months reported in various literatures varies from 20 to 35 percent with a sustained

SIDE EFFECTS DURING THERAPY (N=350)

Adverse Effect	Number n=350	Percent
Influenza like symptoms	320	91.42
Gastrointestinal	310	88.57
Haematological (mild anaemia, leucopoenia, thrombocytopenia	280	80.00
Dermatological (dry skin, pruritis, itching, erythema at the site of injection	285	81.42
Cognitive impairment (Liability of mood, anxiety, depression, insomnia	250	71.42
Myopothaie	3	0.85
Retinopathie	2	0.57
Major depression	2	0.57
Thyrotoxicosis	2	0.57
Suicide attempt	2	0.57

TABLE–4

virological response of 15 to 20 percent, which can be further increased up to 30 to 35 percent when the treatment is prolong for 12 months.[18,19] Addition of ribavirin to interferon enhances the therapeutic response rate.

The mechanism of antiviral action of ribavirin seems to be related to inhibition of the viral RNA- dependent RNA polymerase by depleting intracellular guanine pools and by interfering with the "capping" of viral RNA[20]. The antiviral effect of Ribavirin alone does not seem to be impressive in chronic HCV infection[15,21]. The enhanced effect of interferon and ribavirin in combination could be explained by a synergistic antiviral effect on HCV, as has been shown in vitro with other RNA viruses[22]. The exact mechanism of this synergistic antiviral effect is presently unknown.

The ALT level decreased to normal in 74.2% of patients at the end of four weeks of treatment and 90% of patients at the end of twelve weeks of treatment. HCV RNA was cleared in 78.5% of patients at the end of twelve weeks and 85.14% of the patients at the end of twenty-four weeks. This delayed clearance of HCV RNA from serum during combination therapy is frequently associated with sustained response. This phenomena is unknown with patients who are treated with interferon alone, which suggests that stopping therapy at 12 weeks because of persistent viraemia as suggested [1,23,24] may not be appropriate in the case of therapy with interferon and ribavirin.

In our study the response rate to combination therapy of interferon plus ribavirin for 6 months is 85.14%. During the 6 months follow up treatment 76.5% of the patients had persistently normal ALT and negative HCV RNA.

Our study supports a number of earlier studies[1,12,18,20,25] which showed that combination of interferon plus ribavirin is more effective than interferon alone both in term of initial and sustained response. Ming and colleagues[26] have reported 76% initial response rate at the end of 24 weeks therapy and 34% sustained response rate. Similarly, John and co-workers have reported a response rate of 53% to combination therapy for 6 months with sustained virological response of 31%. Javid and colleagues[27] reported a response rate of 87.83% with combination therapy of interferon and ribavirin in Pakistani HCV patients. Similarly a sustained virological response of 71.4% has been reported by Wazir et al[28] with the combination therapy. According to Shafi et al[29] the response rate to combination therapy was 65%. The low response rate reported by Ming et al and John et al may be due to the fact that Genotype 1b is predominant in Europe which is associated with severe clinical course of the disease and a decreased response to treatment where as in Pakistan the predominant type is Genotype

3 (3a and 3b)[30-32], which has a slow progression of the disease and a good response treatment.

CONCLUSION

In conclusion, our study shows that treatment of chronic HCV patients with combination therapy of interferon and ribavirin had excellent sustained viral and biochemical response with 24 weeks treatment and offers a chance of sustained response and 2) the side effects have been tolerable and manageable.

REFERENCES

1. National Institute of Health Consensus statement; management of hepatitis C. Hepatology 2002; 36 (Supple I):51-20.
2. Takahashi M, Yamada G, Miyamoto R, et al. Natural course of chronic hepatitis C. Am J Gastroentrol 1993; 88: 240-43.
3. Chen DS. Hepatitis B and C virus infections in hepato cellular carcinoma and their prevention In: Nishioka K, Suzuki H, Mishiro S, Oda T, editors. Viral hepatitis and liver disease . Tokyo: Springer verlag; 1994: 685-9.
4. Alter MJ. Epidermialogy of Hepatitis C. Hepatology 1997; 26: (suppl 1):625-55.
5. Terrault NA, Wright TI. Hepatitis C virus in the setting of transplantations. Semin Liver Dis 1995; 15:92-100.
6. Hoofnagle JH, Mullen KD, Jones BD, et al. Treatment of Chronic non A non B hepatitis with recombinant human alpha interferon: Preliminary report N Engl J Med 1986, 315:1575-8.
7. Fried MW, Hoofnagle JH. Therapy of hepatitis C. Semin Liver Dis 1995; 15: 82-91.
8. Tine F, Margin S, Craxi A, Pagllaro L. Interferon for non A, non B chronic hepatitis. A meta analysis of randomized clinical trials. J Hepatol 1991; 13:192-9.
9. Saracco G, Risina F, Abate ML, et al. Long term follow up of patients with chronic hepatitis C treated with different doses of interferon alpha 2b. Hepatology 1993; 18:1300-5.
10. Marcellin P, Boyer N, Degott C, et al. Long term histological and viral changes its patients with chronic hepatitis C, who responded to alpha interferon Hepatology 1994; 14: 302-7.
11. Carithers RL-JR, Emerson SS. Therapy of Hepatitis C: Meta-analysis of interferon alpha2b trials. Hepatology 1997; 26(3 suppl): 835-8s.
12. Poynard T, Bedossa P, Chevallier M, et al. A comparison of three Interferon alpha 2b regimens for long terms treatment of chronic non A, non B hepatitis. N Engl J Med 1995; 332:1457-62.
13. Di Bisceglie AM, Shindo M, Frong TL, et al. A pilot study of ribavirin therapy for chronic hepatitis C. Hepatology 1992;16: 649-54.
14. Fernandez H, Banks G, Smith R. Ribavirin: a clinical over view Eur. J Epidermal 1986; 2:1-14.
15. Reichard O, Andersson J, Schvarcz R, Weiland O. Ribavirin treatment for chronic hepatitis C, Lancet 1991; 337:1058-61.
16. Reichard O, Norkrans G, Fryden A, et al. Randomized double blind, placebo controlled trial of interferon alpha 2b with and with out ribavirin for chronic hepatitis C. Lancet 1998; 351:83-7.
17. Selivarez R, Yun ZB, Sonnerborg A, Weiland O. Combined treatment with interferon alpha 2b and ribavirin for chronic hepatitis C in patients with previously non response or non sustained response to interferon alone. J Med Virol 1995; 46:43-7.
18. Mc Hutchinsum JG, Straut C, Gordan, et al. Interferon alpha 2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. N Engl J Med 1998; 339: 1485-92.
19. Giuseppe B, Gabriella DL, Maurizio S, et al. Interferon 2b and ribavirin in combination

for chronic hepatitis C. Patients not responding to interferon alpha alone. An Italian multicenter, randomized, controlled Clinical trial. Am J Gastroenterol 1998; 39:2445-51.

20. Patterson JL, Fernandez-Larsson R. Molecular mechanism of action of ribavirin. Rev Infect Disease 1990; 12:1132-46.

21. Bodenheiner HC Jr, Lindsay KL, Davis GL, et al. Tolerance and efficacy of oral ribavirin treatment of chronic hepatitis C: A multicenter trial. Hepatology 1997; 26:473-7.

22. Hayden FC, Schlepushkin AN, Pushkarskaya NL. Combined interferon alpha 2, amantadin hydrochloride and ribavirin inhibition of influenza virus replication in vitro. Anti micro Agents Chemother 1984; 25:53-7.

23. Tang MJ, Blatt IM, Mc Hutchinson JG, et al. Prediction of response during interferon alpha 2b therapy in chronic hepatitis C patients using viral bio-chemicals: a comparison. Hepatology 1997; 26: 1640-5.

24. Mc Hutchinson J, Blatt L, Sedghi VA, et al. Is there an optimal time to measure quantitative HCV RNA to predict non response following interferon treatment for chronic HCV infection? J Hepatol 1998;29:362-8.

25. Poynard T, Marcelein P, Lee SS, et al. Randomised Trial of interferon alpha 2b plus ribavirin for 48 weeks or 24 weeks versus interferon alpha 2b plus placebo for 48 weeks for treatment of chronic hepatitis C virus. International Hepatitis Interventional therapy Lancet 1998; 352: 1426-32.

26. Ming YL, Jia HK, Pei MY, et al. Long term efficacy of ribavirin plus interferon alpha in the treatment of chronic hepatitis C. Gastroenterology 1996; 111: 1307-12.

27. Farooqi JI, Farooqi RJ, Hameed K. Interferon, 2b mono therapy and in combination with ribavirin as initial treatment for chronic hepatitis C. J Coll Physic Surg Pak 2002; 12:82-5.

28. Wazir MS, Majid AS, Solangi GA, Zuberi BF. Role of interferon and interferon plus ribavirin in the management of chronic hepatitis C. J Coll Physic Surg Pak 2002;12:609-612.

29. Shafi MS, Ahmad SI, Rehana M, Mustafa G. Daily interferon versus interferon TIW in combination with ribavirin for treatment of chronic hepatitis C. J Rawal Med Coll 1999;31:20-2.

30. Idrees M. Common genotypes of hepatitis C virus present in Pakistan. *Pak J Med Res* 2001; 40: 46-9.

31. Idrees M. Comparison of two systems: Murex HCV serotyping 1-6 assay and genotype-specific PCR for hepatitis C virus genotyping. J Coll Physic Surg Pak 2000; 11: 22-5.

32. Idrees M. Detection of six serotypes of HCV in anti-HCV positive patients and rate of ALT/AST abnormalities. *Pak J Microbial*, 2001; 61-5.

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