INTERFERON-RIBAVIRIN TREATMENT IN CHRONIC HEPATITIS C– THE LESS TALKED ABOUT ASPECTS

Shahid Raza Khalid, Anwaar A Khan, Altaf Alam, Nasir Hassan Lak, Arshad Kamal Butt, Farzana Shafqat, Aftab Alvi, Irfan Ahmed, Shahid Sarwar, Amir Niazi

Department of Gastroenterology, Hepatology Shaikh Zayed Postgraduate Medical Institute Lahore, Pakistan

Background: Combination therapy with interferon and ribavirin has become the standard of care in the treatment of Chronic Hepatitis C (CHC) infected patients. Treatment response, however, is not 100% and is accompanied with side effects faced by the patient as well as observed in haematologic indices. Studies are focusing on daily or high-dose induction therapy with interferon, the titration of interferon dosing to initial viral load, higher doses of interferon throughout treatment, and adjustment of interferon dosing to the viral responses. The safety and efficacy of these approaches have not been sufficiently established. Objectives were to see the response of 2 different dosage regimens, effects and side effects and to assess the efficacy and side effects of 2 treatment regimens of Interferon and Ribavirin in CHC. **Methods:** A total of 32 patients with CHC at Department of Gastroenterology and Hepatology, Shaikh Zayed Postgraduate Medical Institute Lahore from June 2001 to February 2003 were included in the study and were divided into two groups for treatment. Group A (14 patients) received 5 MU of injection Interferon alpha 2 b S/C daily for 2 weeks followed by 3 MU thrice weekly for the next 22 weeks. Group B (18 patients) received injection interferon alpha 2 b 3 MU S/C thrice weekly for 24 weeks. Ribavirin therapy was started at 1200 mg daily in 3 divided doses and later modified according to side effects. Patients were evaluated at 2, 4, 8, 12, 16, 20 and 24 weeks during the therapy and then 24 weeks after the completion of treatment. **Results:** Out of 32 adult patients included in the study, 18 were males and 14 females. Haemoglobin was more than 12 gm/dl in females and more than 13 gm/dl in males, WBC count was more than 3.0×10^9/L and Platelet count was more than 100×10^9/L. Twenty patients completed 6 months combination treatment, 16 reported with their end of treatment HCV RNA PCR results, 8 from each group. Twelve patients were lost to follow up. End of treatment response (ETR) in group A was 88% and 62.5% in group B. Sustained virological response in group-A was 5/8 (62.5%) and 4/5 (50%) in group-B. The frequency and severity of flu like symptoms like fever, body aches, skin rash, hair loss, cough and psychiatric symptoms were more in group A than in group B. There was no significant difference in the 2 groups for haematologic side effects. **Conclusions**: Treatment with 5 MU interferon daily for initial two weeks followed by 3 MU thrice weekly for 22 weeks is more effective than 3 MU thrice weekly for 24 weeks but with more side effects.

Keywords: Hepatitis, Chronic Hepatitis C, Interferon, Ribavirin, Therapy, Side effects

INTRODUCTION

Hepatitis C has a world wide distribution with a prevalence of 250 million, i.e., 3% of the world population.[1] Its prevalence in Pakistan varies widely, but generally is in the range of 3–13%.[2,3] The treatment of CHC is now well established with conventional interferon or pegylated interferon in combination with ribavirin.[4] Various regimens with different doses and duration of treatment continue to be investigated to optimize the treatment.[3] In Pakistan with predominance of genotype 3 combination of conventional interferon and ribavirin continues to be used widely. Data regarding efficacy of the combination treatment in our region has been clearly demonstrated in various studies but the side effects of this treatment have not been studied in great detail and data remains scarce. This study has been planned to highlight the efficacy as well the side effects of interferon-ribavirin combination in two different dose regimens in the treatment of CHC.

PATIENTS AND METHODS

A total of 32 adult patients were included in the study during the period June 2001–Feb 2003 in the Department of Gastroenterology/Hepatology at the Shaikh Zayed Postgraduate Medical Institute Lahore, 18 were males and 14 were females. All these patients were 18–65 years old, treatment naïve, compensated liver disease hepatitis 'C' RNA positive, genotype 3 with elevated ALT. None of the patients had significant psychiatric history or cardiovascular disease.

Included patients were divided into two groups for treatment. Group A (14 patients) received 5 MU of injection Interferon alpha 2b S/C daily for 2 weeks followed by 3 MU thrice weekly S/C for next 22 weeks. Group B (18 patients) received injection Interferon alpha 2 b S/C thrice weekly for 24 weeks. Both groups were given Ribavirin 1200 mg daily in 3 divided doses. Ribavirin therapy was started at 1200 mg daily in 3 divided doses, later modified according to the side

effects. Patients were evaluated at 2, 4, 8, 12, 16, 20, 24 weeks during therapy and then 24 weeks after completion of treatment.

End of treatment response was defined as negative HCV RNA by PCR and normal ALT at the end of the treatment. Sustained viral response was defined as negative HCV RNA by PCR and normal ALT at 24 weeks after stopping the treatment. At each visit complete blood count (CBC), platelet count and ALT were checked. Thyroid functions were checked before the start of treatment, at week 12 treatment and at 24 weeks after stopping the treatment. At each visit any side effect were recorded and graded according to modified WHO guidelines as mild, moderate, severe and life threatening.

Method used for HCV RNA PCR was by RT-PCR using Amplicor HCV Monitor kits on Cobra Amplicor Analyser (Roche Diagnostic Systems USA).

Data was analysed using SPSS version 13.

RESULTS

A total of 32 adult patients were included in the study, 18 were males and 14 females. Haemoglobin was more than 12 gm/dl in females and more than 13 gm/dl in males, WBC more than 3.0×10^9/L and platelet count more than 100×10^9/L. Twenty patients completed 6 months combination treatment, 16 reported with their end of treatment HCV RNA PCR results, 8 from each group, and 12 patients were lost to follow up.

Table-1: Patients' demography and base line features

Total No of patients	32
Males	18
Females	14
Mean age (years)	33.1±10.6, range 18–65
Treatment status	Treatment naive
Psychiatric history	No significant psychiatric disease
Cardio vascular disease	No significant cardiovascular disease
HCV RNA	Positive
Genotype	3a
ALT IU/L	Mean 143.6 (SD±25.3)
Hb (g/dl)	Mean 13.7g/dl (SD±0.3)
Platelet count 10^9	Mean 200 (SD±20)
Neutrophil	Mean 63 (SD±5)

ETR was achieved in 12, 7/8 (88%) from group-A and 5/8 (62.5%) from group-B. Four (2 males and 2 females) did not respond. ETR in group-A was 88% and in group-B it was 62.5%. Sustained virological response was 5/8 (62.5%) in group-A, and 4/5 (50%) in group-B.

The frequency and severity of the flu like symptoms like fever, body aches, skin rash, hair loss, cough and psychiatric symptoms were more frequent in group-A than in group-B (Table-2).

Table-2: Frequency of side-effects in two treatment groups

Side Effects	Frequency	
	Group A	Group B
Flu like	(10%)	(5%)
Fever	(8%)	(6%)
Body aches	(20%)	(5%)
Skin Rash	(6%)	(3%)
Hair loss	(12%)	(7%)
Cough	(8%)	(6%)
Psychiatric symptoms	(13%)	(10%)

Psychiatric side-effects were more frequent in group-A than in Group-B (13% vs 10%). In one patient in group-A, treatment had to be stopped because of severe depression and suicidal tendency.

The platelet count registered an increase towards the end of the study in group-B ($p<0.001$), and it remained steady in group-A. The difference among both the groups was significant at the end of the treatment ($p>0.001$). Both groups registered a transient drop in neutrophil count during the start of treatment, group-A more than group-B. About 1% of patients exhibited neutrophil counts $<0.5\times10^9$ cells/L. However the reduction in WBC and neutrophil counts were transient with no clinical significance, and returned to normal following completion of treatment with no significant difference among the 2 groups.

Haemoglobin also dropped by 2 g/dl during the treatment. Statistically significant fall in Hb was seen in both the groups. In group-A from 14 g/dl pre-treatment to 13 g/dl at 24 weeks of treatment ($p<0.01$), and in group-B from 13.4 g/dl pre-treatment to 12.7 g/dl at 24 weeks of treatment ($p<0.001$). There was no significant difference in the fall of haemoglobin between the 2 groups. Rest of the haematologic indices did not show any significant differences.

The pre-treatment ALT levels were high, mean in group-A was 188.8±27.7 IU/L, and in group-B it was 98.5±22.9 IU/L. Drop in ALT level, was more in group-A than group-B at the end of 6 months treatment. The difference among the groups was not statistically significant.

End of treatment biochemical response in group-A was 89% and 84% in group-B. Overall biochemical response was better than virologic response.

DISCUSSION

Combination therapy with ribavirin and interferon alpha-2b is approved for the treatment of patients with CHC who have compensated liver disease.[6–8] The optimal dose and interval for administering interferon therapy continues to be investigated. Studies are focusing on the efficacy of daily or high-dose induction therapy with interferon, the titration of interferon dosing to initial viral load, higher doses of interferon throughout treatment, and adjustment of interferon

dosing to the viral response.[6–13] The safety and efficacy of these approaches have not been sufficiently established. Based on this evidence we used induction therapy for the first two weeks in group-A.

Combination therapy with ribavirin and interferon alpha-2b is associated with a number of potentially dose-limiting side effects, most symptoms can be managed with medical intervention and dose reduction.

The withdrawal rate increases with both the duration of treatment and use of combination therapy.[13] For example, therapy was stopped in 13–14% of patients treated with interferon mono therapy for 48 weeks[11] compared with 19–21% of patients receiving combination therapy for the same duration. The withdrawal rate for combination therapy was lower when therapy was administered for only 24 weeks (8%).[12]

Serious (grade-3) and life threatening (grade-4) adverse events were reported in (17%) patients in the randomised controlled trials. The more clinically significant serious adverse event categories were psychiatric (1.1%), cardio-vascular (0.9%), gastrointestinal (0.6%), respiratory (0.4), and skin disorders (0.1%). The only life threatening adverse event reported in our study was neutropenia in 1% of our patients. However the neutropenia was not associated with adverse clinical squeal (e.g., infection). This finding is commensurate with other studies.[15]

The dose-limiting toxicity of ribavirin is a reversible, normochromic, normocytic, haemolytic anaemia. Mechanism is still unknown, however ribavirin accumulates to a much higher degree (60–70-fold)[16] in non-nucleated cells (i.e., erythrocytes) than in nucleated cells.[16] Regardless of the mechanism(s) underlying anaemia, Hb levels decrease from baseline within the first 2–4 weeks of combination therapy.

Serious side effects are not more common with combination treatment that with interferon monotherapy.[17] In our study statistically significant fall in Hb was seen in both the groups, however, there was no significant difference among the 2 groups.

Alpha interferon has myelosuppressive effects, which may be attributed to this cytokine's anti-proliferative activity on haematopoietic progenitor cells.[18] Alpha interferon therapy commonly results in mild decreases in Hb concentration, WBC count, and platelet count. In patients who initiate combination therapy with normal WBC and platelet counts, the reduction in concentration of theses parameters has not been associated with complications, such as bacterial infection or bleeding episodes. There was no significant difference in the 2 groups for haematologic side effects except for platelet count which increased in many of the patients.[7,18] The platelet count registered an increase towards the end of the study in Group-B but remained steady in Group-A.

The incidence of psychiatric adverse events was 13% in Group-A and 10% in Group-B. In one patient in Group-A, treatment had to be stopped due to suicidal tendency. In other studies psychiatric adverse events were reported by >20% of patients, dose limiting events were seen in 8.5%.[19,20] The mechanism underlying the adverse neuropsychiatric effects of alpha interferon are poorly understood. It is well recognised that the blood-brain barrier is essentially impermeable to interferon, though interferon may permeate the circumventricular organs, and exert effects on central nervous system via these regions.[21,22] The hypothesis that the incidence of alpha interferon induced depression increases disproportionately with the duration of treatment is not supported by the studies[18,19], whereas our study suggests that dose may have an effect on the incidence of psychiatric adverse events but it needs further randomized controlled trials to reach a conclusion. A role for antidepressant support for patients receiving, combination therapy has not been established at this time.[20]

CONCLUSION

In our study response of group-A to combination therapy of CHC was better than group-B with higher incidence of tolerable side effects. Haematologic indices showed variation in response to the combination treatment but the biochemical profile (excluding ALT) did not show any significant change.

REFERENCES

1. WHO. Global surveillance and control of hepatitis C. Report of WHO consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium. J Viral Hept 1999;6:35–47.
2. Amin J, Yousaf H, Mumtaz A, Iqbal M, Ahmed R, Zaman S, *et al.* Prevalence of hepatitis B surface antigen and anti hepatitis C virus. Professional Med J 2004;11:334–7.
3. 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.
4. Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. AASLD practice guide lines. 2004 Available at: http://www.natap.org/2004/pdf/AASLD_Prac._Guide_Hep_C.pdf
5. Peine, CJ, Albracht, JK, Rizel, JP, Gershwin E, Ansari M, Aftab A. *et al.* A comparison of standard and induction interferon therapy with and without initial ribavirin in treatment of naïve patients with chronic hepatitis C. Hepatology 2000;32:364A.
6. Carithers, RL, Manns, MP, Pemillow, RP, Dickson R, Jorgensen R, Petz JL. *et al.* Multicenter, randomized, controlled trial comparing high dose daily induction interferon plus ribavirin versus standard interferon alfa-2 B plus ribavirin. Hepatology 2000;32:317A.
7. Poynard T, Bedossa P, Chevallier M, Mathurin P, Lemonnier C, Trepo C, *et al.* A Comparison of three alfa-2b interferon regimens for the long term-treatment of chronic non-A, non-B hepatitis. N Engl J Med 1995;332:1457–62.

8. Shindo M, Aria K, Sokawa Y, Okuno T. Hepatic hepatitis C virus RNA as a predictor of long- term response to interferon alpha therapy. Ann Intern Med1995;122:586–91.
9. Afdhal, NH, Brand, M, Epstein, A, Massimo R, Colombo P, Borzio M. *et al*. Randomized controlled trial of interferon-A (Interon A) 5 MU daily plus ribavirin 1000 mg daily versus interferon-A (Interon A) 3 MU TIW plus ribavirin 1000 mg daily in patients with HCV who have never received precious therapy. Hepatology 2000;32:363A.
10. Marcellin P, Boyer N, Gervais A, Martinot M, Pouteau M, Castelnau C, *et al*. Long-term histologic improvement and loss of detectable intrahepatic HCV RNA in patients with chronic hepatitis C and sustained response to interferon-alpha therapy. Ann Intern Med 1997;127:875–81.
11. McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, *et al*. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. N Engl J Med 1998;339:1485–92.
12. Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS, Ideo G, *et al.* Randomized trial of interferon alfa-2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alfa-2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. Lancet 1998;352:1426–32.
13. Poynar T, Leroy V, Cohard M, Thevenot T, Mathurin P, Opolon P, *et al.* Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration. Hepatology 1996;24:778–89.
14. Davis GL, Balart LA, Schiff ER, Lindsay K, Bodenheimer HC Jr, Perrillo RP, *et al.* Treatment of chronic hepatitis C with recombinant interferon alpha. A multicenter randomized, controlled trial. Hepatitis interventional therapy group. N Engl J Med 1989;321:1501–6.
15. Lertora JJ, Rege AB, Lacour JT, Ferencz N, George WJ, VanDyke RB, *et al.* Pharmacokinetics and long-term tolerance to ribavirin in asymptomatic patients infected with human immunodeficiency virus. Clin Pharmacol Ther 1991;50:442–9.
16. Page T, Connor JD. The metabolism of ribavirin in erythrocytes and nucleated cells. Int J Biochem 1990;22:379–83.
17. Schalm SW, Hansen BE, Chemello L, Bellobuono A, Brouwer JT, Weiland O, *et al.* Ribavirin enhances the efficacy but not the adverse effects of interferon in chronic hepatitis C. A meta-analysis of individual patients data from European centers. J Hepatol 1997; 26:961–6.
18. Dusheiko G Side effects of alpha interferon in chronic hepatitis C. Hepatology 1997;26(suppl 1):112S–121S.
19. Levenson JL, Fallon HJ. Flouxitine treatment of depression caused by interferon-alpha. Am J Gastroenterol 1993;88:761–1.
20. Valentine AD, Meyers CA, Kling MA, Richelson E, Hauser P. Mood and cognitive side of interferon-a therapy. Semin Oncol 1998;25(Suppl 1):39–47.
21. Meyers CA, Scheibel RS, Forman AD. Persistent neurotoxicity of systemically administered interferon-alpha. Neurology 1991;41:672–6.
22. Wiranowska M, Wilson TC, Thompson K, Prockop LD. Cerebral interferon entry in mice after entry in mice after osmotic alteration of blood-brain barrier. J Interferon Res 1989;9:353–6.

Address for Correspondence:

Lt. Col. Dr. Shahid Raza Khalid, Department of Medicine, Combined Military Hospital, Sialkot, Pakistan. **Tel:** +92-52-5716170/Ext: 227, **Cell:** +92-321-5126452
Email: shahidrazakhalid@yahoo.co.uk