EFFICACYAND SAFETY OF INTERFERON ALPHA 2 B PLUS RIBAVIRIN COMBINATION IN CHRONIC HEPATITIS C PATIENTS WITH PULMONARY TUBERCULOSIS

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ABSTRACT

Objective: To assess the efficacy of combination therapy of interferon alpha-2b plus Ribavirin in patients of chronic hepatitis C and pulmonary TB

Material and Methods: This retrospective study comprised of personal series of patients in Gastroenterology Unit, HMC Peshawar and Saidu Group of Teaching Hospitals Swat, from June 1999 to December 2002. Records of chronic hepatitis C and pulmonary TB, were analyzed for base-line parameters, response rates, and any adverse effects. Standard anti-TB was given uninterrupted along with close monitoring of all the patients.

Results: This study was conducted on 22 males and 11 females (33 patients) with chronic hepatitis C and pulmonary tuberculosis.

End-treatment response: serum ALT levels became normal in 18 out of 22 male patients (81.81%), as compared to 10 out of 11 female patients (90.90%), ($P > 0.05$). Serum HCV-RNA became negative in 17 out of 22 male patients (77.27%), as compared to 9 out of 11 female patients (81.81%), ($P > 0.05$).

Sustained viral response: Serum ALT levels remained normal and HCV-RNA PCR remained undetectable at the end of 6 months follow-up period in 15 out of 22 male patients (68.18%), as compared to 8 out of 11 female patients (72.72%), ($P > 0.05$).

Conclusion: We conclude that Interferon plus Ribavirin combination therapy is an effective and safe therapy in the treatment of chronic hepatitis C patients having pulmonary TB.

Key words: Chronic hepatitis C, Pulmonary TB, Interferon, Ribavirin

INTRODUCTION

One hundred and seventy million of world's population is infected with hepatitis C[1,2], 80% having chronic hepatitis and 20% cirrhosis and its sequale[3-7]. HCV infection has become the most common cause of chronic liver disease in America, Europe, Australia[1,8], as well as in Pakistan[9-15].

Combination of Interferon and Ribavirin has increased sustained virological response two-fold as compared to Interferon monotherapy, thus reducing relapse rate[16-20]. The mechanism by which this enhancement of activity occurs with combination therapy is not clearly known[21].

Pulmonary TB is not uncommon in our set up, which needs complete treatment with anti-TB drugs. The scenario becomes somewhat complex when pulmonary tuberculous patients are suffering from chronic hepatitis C as well because now the patient is in need of two types of therapies: anti-TB drugs and anti-HCV drugs. Not only tuberculous patient is chronically ill with low immunity and anemia, but anti-TB drugs are known to affect liver adversely resulting in drugs-induced hepatitis as well. Chronic hepatitis C also results in chronic ill health, and on the top of that, recommended antiviral drugs do lower immunity and result in anemia. Therefore, the present study was conducted to assess efficacy and safety of combination therapy of Interferon alpha-2b plus oral Ribavirin in patients with chronic HCV having pulmonary TB and on standard regimen of anti-TB drugs.

MATERIAL AND METHODS

Records of 33 chronic HCV hepatitis having pulmonary TB and on standard regimen of anti-TB drugs, who were treated with combination of interferon alpha plus oral Ribavirin by the authors from June 1999 to June Dec 2002, were analyzed for the following baseline parameters:

Age of the patients,

Sex of the patients,

Serum ALT levels at the start of treatment,

Presence or absence of liver cirrhosis as evidenced clinically and by ultrasound and / or liver biopsy,

Histopathological status of the patients (if available),

Hematological status of the patients, including hemoglobin, TLC, DLC, and platelet count, etc.

All studied patients were HCV-RNA positive by PCR with raised serum ALT levels. Quantitative PCR, genotyping, and histological status were not known in any of the studied patients. None of the patients were cirrhotic as determined clinically and by ultrasound. None of the patients was co-infected with HBV.

All studied patients had received Interferon alpha at a dose of 3 million units, subcutaneously, three times a week in combination with Ribavirin 400mg, three times, daily for 6 months. All patients were assessed in an outpatient setting for safety, tolerance and efficiency during treatment period. Hematological testing (including hemoglobin, TLC, platelet count) was done weekly during first month, fortnightly during 2nd and 3rd month, and monthly during the remaining period.

All the patients were diagnosed cases of pulmonary TB and had been started on standard regimen of anti-TB drugs i.e Rifampicin, Isoniazid, Ethambutol (all given for six months), and Pyrazinamide (given during initial two months). None of the patients developed pulmonary TB during antiviral therapy; as said before, all were already diagnosed cases of pulmonary TB. All the patients were closely monitored for any evidence of drugs-induced hepatitis, in addition to their monitoring for antiviral therapy.

For consistency with other reports and current clinical practice, we adopted conventional definitions of national institute on hepatitis C[22]. These include:

End Treatment Response: defined as normal serum ALT levels and undetectable serum HCV-RNA levels at the end of therapy.

Sustained Viral Response: defined as a response that persists for at least six months after the stoppage of successful therapy.

Statistical Analysis: Statistical analysis was carried out by using student's t-test for the comparison of means and chi-square test for the comparison of proportions. P value of less than 0.05 was considered to be significant.

RESULTS

Baseline Characteristics:

Thirty-three patients were studied, 22 males and 11 females (Male: Female ratio of almost 2:1). Both gender groups were comparable regarding different baseline characteristics, as shown in Table-1.

End Treatment Response (ETR):

Serum ALT levels: Serum ALT levels became normal in 18 out of 22 male patients (81.81%), as compared to 10 out of 11 female patients (90.90%), ($P > 0.05$), as shown in Table-2.

BASELINE CHARACTERISTICS OF PATIENTS

Characteristics	Males	Females
-Male/Female	22	11
-Mean Age (yrs)±SD	39±3	35±6
-*Mean serum ALT levels (IU) ±SD	108±11	93±12
-*Mean Hb (gm%) ±SD	11.7±0.3	11.3±0.4
-*Mean TLC/cm3±SD	9342±640	9035±235
-*Mean platelet count ±SD	202345±6000	164240±6000
-Presence of cirrhosis	Nil	Nil

Table 1

SD= Standard Deviation, ALT= Alanine Aminotransferase
* At the time of stating treatment.

HCV-RNA: Serum HCV-RNA became negative in 17 out of 22 male patients (77.27%), as compared to 9 out of 11female patients (81.81%), (P > 0.05), as shown in Table-2.

Therefore, according to two parameters, ETR was found to be 77.27% in male patients and 81.81% in female patients.

- Sustained Viral Response (SVR):

  Serum ALT levels remained normal and HCV-RNA PCR remained undetectable at the end of 6 months follow-up period in 15 out of 22 male patients (68.18%), as compared to 8 out of 11 female patients (72.72%), (P > 0.05), as shown in Table-2.

- Discrepancies between response parameters:

  Discrepancies between serum HCV-RNA responses and the serum ALT responses to interferon treatment have been reported23. In the present study, serum HCV-RNA levels remained detectable after treatment despite persistently normal serum ALT levels in 3 out of 22 male patients (13.63%), as compared to 1 out of 11 female patients (09.09%), (P > 0.05). In contrast, in all patients in whom serum HCV-RNA levels became undetectable, had normal serum ALT levels as well; this is in contrast to others24.

- Correlation of Baselines Characteristics with Response:

  Age, sex serum ALT levels, and other hematological parameters at the start of treatment did not influence the rate of response, comparable to others23.

- Adverse Events:

  The type and frequency of adverse events were similar in both gender groups and reflected the known safety profile of interferon; febrile feeling, nausea, insomnia, anorexia and rash were more common. None of these were treatment limiting. No patient died.

  Ribavirin accumulates in red cells and results in hemolysis[25]. Hemoglobin concentration dropped during the first month of treatment by 0.9 to 2.3 gm per patient, remained stable thereafter; and returned to near baseline values after the cessation of treatment. Compensatory reticulocytosis was noted in all these patients. Concomitant rises in serum uric acid and bilirubin of mild severity also occurred with hemolysis. Hemoglobin concentration fall was less in male patients as compared to female patients, but statistically not significant (P > 0.05).

  Leukocyte and platelet count decreased in both the gender groups during therapy, but remained within normal range except in four patients: 3 male and 1 female. The respective treatment was temporarily discontinued for 3 to 12 days in these patients, where it was restarted after restoration of leucocytes and / or platelets count.

  Neither any of the patients developed drugs-induced hepatitis nor antiviral therapy has to be stopped in any of the patients because of any serious side effects.

DISCUSSION

All the patients were diagnosed cases of pulmonary TB and had been started on standard regimen of anti-TB drugs i.e Rifampicin, Isoniazid, Ethambutol (all given for six months), and Pyrazinamide (given during initial two months). None of the patients developed pulmonary TB during antiviral therapy; as said before, all were already diagnosed cases of pulmonary TB. All the patients were closely monitored for any evidence of drugs-induced hepatitis, in addition to their monitoring for antiviral therapy. This study confirms that the combination of Interferon-alpha and Ribavirin for 6 months is an effective and safe therapy for patients of chronic HCV hepatitis who are also suffering from pulmonary TB and taking anti-TB drugs like Rifampicin, Isoniazid, Ethambutol, and Pyrazinamide. The efficacy is in terms of normalization of serum ALT levels and HCV-RNA clearance at the end of treatment (end-treatment response) and at the end of 6 months follow-up period (sustained response) is greater as

RESPONSE IN THE PATIENTS

Parameters	Males (n=22)	Females (n=11)	P-value
-Normalization of ALT	18/22 (81.81%)	10/11 (90.90%)	P > 0.05
-Loss of HCV-RNA	17/22 (77.27%)	09/11 (81.81%)	P > 0.05
-End Treatment Response	17/22 (77.27%)	09/11 (81.81%)	P > 0.05
-*Sustained Response	15/22 (68.18%)	08/11 (72.72%)	P > 0.05

Table 2

* Defined as normal serum ALT levels as well as negative HCV-PCR at the end of 6 months of follow up.

compared to other studies [21, 24, 26], the reason may be that HCV genotype 3 is the most prevalent type in our set-up[26].

Histological status on liver biopsy was not available in any of the studied patients, in contrast to other studies[21,24,26]. Greater improvement in the knodell inflammatory score has been reported with combination regimen as compared to interferon monotherapy[21,24]. Therefore, we also need to analyze this aspect in our patients in prospective type of studies.

HCV genotype, pretreatment serum HCV-RNA levels, and the presence of fibrosis or cirrhosis at baseline (on histology) influence the initial response to treatment with interferon monotherapy[27-30]. A sustained virological response is more common in patients with serum HCV-RNA level of less than 2.5 million copies/ml and HCV genotypes other than type-1[21,24,26-30]; therefore, determination of the viral genotype and the pretreatment serum HCV-RNA level is of great significance. In our series, genotyping and HCV-RNA levels were not known; therefore, we need to evaluate this aspect in further studies as well. It has been reported[16-21] that female patients respond better to combination therapy as compared to male patients; we also noted the same, but statistically the difference in results was not significant. None of our patients was cirrhotic on the basis of clinical features and ultrasound.

Combination treatment regimen was safe and reasonably well tolerated. The only important risk associated with combination therapy was hemolytic anemia. The fall in the hemoglobin concentration occurred during the first month, emphasizing the need for careful monitoring of patients during treatment with Ribavirin.

We conclude from our local experience, that the combination of interferon and Ribavirin is safe and effective for the treatment of pulmonary tuberculous patients with chronic hepatitis C who are already on anti-TB drugs. Female patients respond better to combination therapy as compared to male patients; but statistically the difference in our series was not significant. We need to evaluate different aspects of the issue in further studies.

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