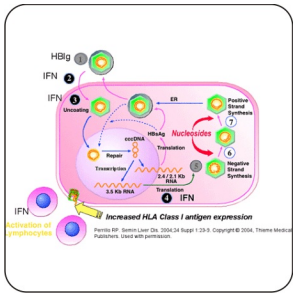
ORIGINAL **PROF-1317**

EFFICACY OF INTERFERON THERAPY IN PATIENTS OF CHRONIC HEPATITIS B VIRAL INFECTION TREATED AT MH RAWALPINDI



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ABSTRACT... Background: The consequences of acute and chronic HBV infection are major public health problems. These infections may progress to cirrhosis, liver failure, and Hepatocellular carcinoma Treatment of chronic replicative hepatitis B virus (HBV) infection is aimed at stopping viral replication and preventing the development of chronic liver disease. **Objective:** To determine the efficacy of Interferon therapy in patients of chronic Hepatitis B treated at MH Rawalpindi, by comparison of PCR for HBV DNA before and after Interferon therapy. **Study Design:** Quasi-experimental study. **Place and duration of study:** Military Hospital, Rawalpindi from July 2003 to December 2005. **Subjects and Methods:** The efficacy of a 4-month course of subcutaneously administered human recombinant interferon Alfa was studied. A total of 50 patients of proven chronic viral hepatitis B with presence of hepatitis B surface antigen and hepatitis B virus DNA (HBV DNA) in the serum were enrolled over the span of 30 months. All patients were treated with 5 mega units of recombinant interferon alfa-2b subcutaneously once daily for 4 months. PCR for HBV DNA was performed at the end of fourth month in treated patients as a predictor of response to interferon therapy. **Results:** The treatment was well tolerated, only in three patients treatment was ceased due to severe depression while none of the other patient required dosage reduction or cessation of treatment because of side effects. In 22 treated persons (44.0%) PCR for HBV DNA becomes negative showed response to treatment. This finding is statistically significant (p less than 0.05). **Conclusion:** Interferon Alfa has significant efficacy in chronic Hepatitis B. Patients of chronic Hepatitis B in whom Interferon therapy is not contraindicated should be treated with Interferon Alfa to avoid long term complication of infection.

Key words: Chronic Hepatitis B, HBV, Interferon Alfa, PCR.

INTRODUCTION

Worldwide, the consequences of acute and chronic HBV infection are major public health problems[1]. It is estimated that approximately 350 million people have

chronic HBV infection[1-6]. Although HBV can be prevented by vaccination, it remains an important cause of morbidity and mortality. The spectrum of clinical manifestations of HBV infection varies in both acute and chronic disease. During the acute phase, manifestations range from subclinical or anicteric Hepatitis to icteric hepatitis and, in some cases, fulminant hepatitis. During the chronic phase, manifestations range from an asymptomatic carrier state to chronic hepatitis, cirrhosis, and Hepatocellular carcinoma. Extrahepatic manifestations also can occur with both acute and chronic infection. About a quarter of carriers develop serious liver disease as a result of the infection, around 1000,000 persons die annually of HBV-related liver disease[1,4]. Viral hepatitis is the major cause of chronic liver disease[1,3,4]. Untreated, these infections may progress to cirrhosis, liver failure, and Hepatocellular carcinoma[1,3,4,7]. Because of these complications, five-year survival rates may be as low as 55 percent[8]. Ultimately, 40 percent of Asian men with chronic hepatitis B die of either complications of cirrhosis or Hepatocellular carcinoma[9]. The objective of treating chronic HBV infection is to halt progression of liver injury by suppressing viral replication or eliminating infection, which will prevent progression to cirrhosis and HCC and prolongation of survival. Interferon therapy causes loss of HBeAg and HBV DNA in approximately a third of treated patients,[1,9,16] and the loss of these markers of active viral replication is associated with improvements in hepatic histology and ALT levels. In general, seroconversion from HBeAg to hepatitis B e antibody (anti-HBe) is associated with disappearance of HBV DNA in serum and remission of liver disease[9]. Improvement is usually sustained well after therapy has been discontinued[4,18-19]. Interferon treatment is an independent factor associated with a 50% reduction in the risk of developing Hepatocellular carcinoma[20]. The effects of Interferon therapy should be monitored clinically, in addition, serum aminotransferase concentrations should be measured at two to four week intervals, with serologic assay for HBV DNA performed at the start of therapy, the end of therapy, and six months later[1,21]. HBV infection is endemic in Pakistan with a difference of frequency in different communities,[22] no authentic data is available,[21] but it is estimated that there are about 9 million hepatitis B carriers in Pakistan[23-25]. In Pakistan significant data about response of Interferon alpha treatment is not available, In two local studies, response to interferon treatment found 46-50%[26,27]. This study is design to evaluate efficacy of Interferon-alpha in chronic hepatitis B infection.

PATIENTS AND METHODS

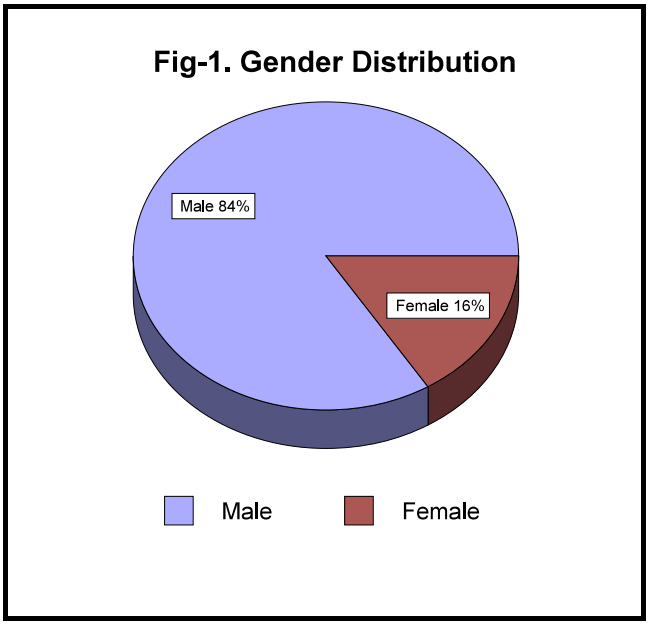
The data was collected from adult patients of all ages with already diagnosed chronic hepatitis B virus infection and positive PCR of HBV DNA, presented at Military Hospital Rawalpindi. Those patients who was already treated with interferon therapy or simultaneously infected with Hepatitis C virus, had other chronic illness like renal failure, cardiac failure, anemia or who had cirrhosis were not included in the study. Data was entered in proforma designed to conduct the study. Detailed clinical examination was performed on every patient to evaluate comorbidity. 50 cases were identified among them 42 (84%) were male and 8 (16%) female, prior promission was sought for sanction of interferon therapy from medical directorate GHQ. Interferon Alfa in the dose of 5 million units subcutaneously daily for four months was administered in all cases and PCR for HBV DNA was perfomed at 0 and 4th months at Armed Forces Institute of Pathology (AFIP) Rawalpindi, using 2nd generation ELLISA technique. Sera were collected from brachial veins of all cases under strict aseptic measures and LFT's and FBC was performed at AFIP Rawalpindi on monthly basis to monitor response to treatment and adverse effects of therapy. Those patients in whom therapy was discontinued due to any reason were excluded from our study. Patients were disposed off as per hospital policy after 4 months. There was no further follow up.

The data was compiled and analyzed by using SPSS version 10 on computer. Rationale descriptive statistics, frequency and percentage were computed for

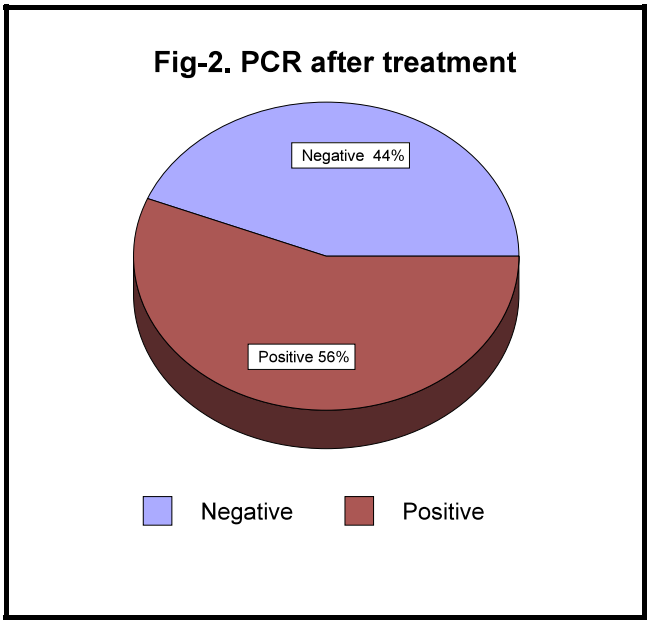
presentation of qualitative variables like sex, laboratory findings like PCR for HBV DNA before and after interferon therapy etc, Mc Nemer test of significance was applied to compare the PCR findings before and after interferon therapy at P<0.05 level of significance. Qualitative variables like age etc, were presented by means ± standard deviation.

RESULTS

A total of 50 patients of proven chronic hepatitis B were enrolled at MH Rawalpindi. The mean age was 36 years with standard deviation from mean being 6.07. The males were 84 % while females being 16 % (Fig-1.).



All of them were treated with interferon Alfa 5 mega units subcutaneously once daily for four months. PCR for HBV DNA was performed at zero and at the end of fourth month in treat group as a predictor of response to interferon therapy. The treat was well tolerated, only in three patients treatment was ceased due to severe depression and they were excluded from study, none of the other patient required dosage reduction or cessatio of treatment because of side effects. In 22 treated persons (44.0%) PCR for HBV DNA becomes negative showed response to treatment (Fig-2.). This finding is statistically significant (p<0.05).



DISCUSSION

In our study we consider PCR for HBV DNA as marker of response to Interferon therapy. In twenty two Out of fifty treated patients (44.0%), Serum HBV DNA levels were below the lower limit of detection, after four months Interferon treatment. This result is statistically significant (P<0.05). Our results are comparable to contemporary studies of Raptopolou M, et al[28]and US National institute of health trials[29]. Another study conducted by Mullar M, et al[30], response was 32.4% with 3 mega units thrice weekly.

Increases in dose and duration of treatment can increase the number of symptoms of toxicity [31-32]. Our results with four months treatment are comparable with six month regimen[28] while HBV DNA clearance occurred in more patients as compared in low dose regimen trial[30].

The tolerability and safety profiles of interferon alfa were satisfactory, and there were no unexpected adverse effects Although depression induced by interferon was

developed in 20 treated patients, only in three out of them, treatment was ceased due to severe depression and they were excluded from study, while in rest of others, it was nothing more than minor feelings of sadness and no patient receiving interferon meet the psychiatric criteria for major depression. These criteria include diminished appetite, weight loss, insomnia or hypersomnia, agitation or mental retardation, fatigue, and diminished ability to concentrate.

The safety profile of Interferon Alpha also compares favorably with the profiles described in previous studies of conventional interferon alfa in patients with chronic hepatitis B[3-34]. It is noteworthy that no patient had hepatic decompensation during treatment.

We observed very trivial side effects like flu like symptoms, nausea, vomiting which observed during initial weeks of treatment, responded well to symptomatic treatment, Di Biscigle observed significant side effect, and even treatment was stopped in few patients due to intensities of side effects[14].

The objective of treating chronic HBV infection is to halt progression of liver injury by suppressing viral replication or eliminating infection, which will prevent progression to cirrhosis and HCC and prolongation of survival. Although most carriers will not develop hepatic complications from chronic hepatitis B, 15-40% develop serious squeal during there life time.

Patients who were successfully treated with interferon Alfa, as indicated by the clearance of HBeAg and HBV DNA (on dot blot hybridization), had a better long-term clinical outcome than those in whom these markers of viral replication persisted. The frequency of death, liver transplantation, and severe clinical complications due to cirrhosis was significantly lower among the patients with elimination of HBeAg than among those with persistence of HbeAg. Our data thus provide further evidence of a benefit of interferon alfa in patients with chronic hepatitis B and may also be used in cost–benefit and cost-effectiveness. Our conclusions about the clinical benefit of the interferon-induced elimination of markers of viral replication are supported by the results of previous studies of the natural history of chronic hepatitis B[36,37,38,39]. The spontaneous seroconversion and HBV DNA elimination is associated with an improvement in the clinical outcome of untreated patients. Nevertheless, the rates of elimination of HbeAg and HBV DNA, as well as of the normalization of alanine aminotransferase levels, were markedly higher among the interferon-treated patients than among the untreated patients. These results have been reported in randomized trials,[34-39] most of which, however, had a considerably shorter follow-up. In previous studies, continued viral replication (persistent HBeAg) was associated with substantial mortality and morbidity during approximately five years of follow-up[39,40]. The benefit to patients in whom HBeAg was cleared after interferon therapy could be due to a selection bias, however, and not to interferon therapy. There is no experimental or epidemiological support for this hypothesis, but the issue cannot be definitely settled, because it would be unethical to withhold long-term treatment with interferon alfa from patients with chronic hepatitis B. Thus, for comparisons, we have to rely on data from patients who remained untreated for a variety of reasons and on data about the natural history of chronic hepatitis B before interferon therapy became available[36-40]. Nevertheless, both types of data support the hypothesis that treatment with interferon improves the clinical outcome, so long as it eliminates HbeAg analyses.

As we did not follow the patients after completion of treatment therefore not able to comment on persistency of seroconversion and recurrence of disease but studies in international literature showed Improvement is usually sustained well after therapy has been discontinued[4,13-17]. Data on long term outcome of patients treated for chronic hepatitis B showed that twenty to fifty percent of long term responders, defined by normal ALT levels and undetectable HBV DNA by hybridization assay cleared HBsAg after five years of follow up[41-43].

We do not have significant numbers of studies to determine efficacy of Interferon in our population. In one study conducted by Sheikh WM, et al[26] response was 46%, which is comparable to our study. Our data thus provide evidence of benefit of interferon alfa in our population with chronic hepatitis B similarly results of our study are comparable to other studies in the international literature.

CONCLUSION

Our study, despite its shortcomings, suggests that, Interferon Alfa has significant efficacy in chronic Hepatitis B. To avoid long term complication of infection, Patients of chronic Hepatitis B in whom Interferon therapy is not contraindicated, should be treated with Interferon Alfa.

To determine the efficacy of interferon in our population, a concerted effort should be made to form a registry of treated patients in our population, to know whether viral replication has been permanently eradicated and the risks for developing the long term sequelae of this disease have truly been reduced.

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