EFFICACY AND COST EFFECTIVENESS OF COMBINED CONVENTIONAL INTERFERON ALPHA 2a AND RIBAVIRIN THERAPY IN PATIENTS OF CHRONIC HEPATITIS C

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ABSTRACT

Objective: *To determine end treatment and sustained virological response to conventional interferons and ribavirin.*

Methodology: *This descriptive study was conducted from January 2009 to September 2011 at DHQ hospital Dir, KPK, Pakistan. Three hundred and forty-seven patients of chronic hepatitis C aged 18 to 60 years were given conventional Interferons alpha 2a and Ribavirin for six months under Prime Minister Program for control of hepatitis.*

Results: *Out of three hundred and forty seven patients three hundred and thirty nine patients completed the therapy. End treatment response was achieved in 229(67.5%) patients and sustained virological response was seen in 210(61.94%) patients.*

Conclusion: *Combination of conventional interferon and ribavirin has a high sustained virological response with fewer side effects in our study. In resource depleted countries like Pakistan, conventional interferon alpha 2a and ribavirin combination therapy can be used as the first line treatment for non affording chronic hepatitis C patients.*

Key Words: *Chronic Hepatitis C, Interferon, Ribavarin*

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INTRODUCTION

Hepatitis C virus infection is major health problem worldwide. WHO estimates that globally 170 million people are chronically infected with hepatitis C, and 3-4 million people are newly infected each year[1]. Acute hepatitis C is an infectious disease affecting the liver and can lead to chronic hepatitis, cirrhosis liver and in 2-6.7 % patients of cirrhosis liver hepatocellular carcinoma over a period of 10-20 years[2]. The current prevalence in Pakistan varies from 3-7 % in different parts of the country[3]. Before the advent of pegylated interferons conventional interferons alpha2a and 2b along with ribavirin was the standard treatment for chronic hepatic C patients[4-6]. With the advent of pegylated interferons conventional interferons alpha 2a and 2b are now no longer used in developed countries. Although pegylated interferons are superior to conventional interferon in many multicentric large scale studies, they are more expensive than conventional interferons. There is no reimbursement or health insurance system in Pakistan. Mostly patients and their family pay for the treatment. Six months treatment with standard interferon and ribavirin cost about US$500 for drugs and US$200 for the follow-up and investigations. Treatment with pegylated interferon and ribavirin costs around US$4000[7]. Developing countries like Pakistan can not afford to treat all patients of chronic hepatitis C with pegylated interferon because of meager resources. As conventional interferons are used in the Prime Minister Program for Hepatitis control in Pakistan, this study is important to know the response of patients with chronic hepatitis C to conventional interferon alpha 2a and ribavirin.

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METHODOLOGY

It was a descriptive study carried out at

DHQ Hospital Dir (upper) from January 2009 to September 2011. Interferon alpha 2b and ribavarin were provided by the Prime Minister Program for Hepatitis Control in Pakistan, although the qualitative PCR were done by the patients themselves from Shuakat Khanum Memorial Cancer Hospital and Research Centre Lahore. Patients aged 18 years and older with chronic HCV infection not previously treated with interferon or ribavirin were included in the study. Eligible patients had abnormal serum amino-transferase concentrations for at least 6 months before the start of therapy with positive HCV antibodies by third generation ELISA and detectable HCV RNA in the serum. Liver biopsy was not performed. Patients under the age of 18 years and above 60 years and those with decompensated liver cirrhosis, were excluded from the study i.e., presence of ascites, bleeding varices, spontaneous bacterial peritonitis, hepatic encephalopathy. Patients having serum albumin lesser than 35g/l, prothrombin time exceeding the normal limits or significant cytopenia were also excluded from the study. Entry hemoglobin values had to be at least 11.5g/dl for women and 12.5g/dl for men. Patients with any other cause of liver disease or other relevant disorders including HIV infection or co-infection with hepatitis B virus, previous organ transplantation, pre-existing psychiatric condition, seizure disorders, cardiovascular disease, haemoglobionopathies, hemophilia and patients with poorly controlled diabetes mellitus and auto-immune diseases were excluded from the study as by the protocols set by the Prime Minister Program for Hepatitis Control in Pakistan. Written informed consent was taken from all the patients. Patients were given combination of interferon alpha 2a plus ribavirin for 24 weeks. All patients received interferon Alfa 2a at a dose of 3 mega units subcutaneously three times a week for 24 weeks. Ribavirin was given orally twice a day to a total dose of 1000mg (body weight lesser than 75 Kg) or 1200mg (body weight more than 75 Kg) per day. All patients were assessed in out patients setting for safety, tolerance and efficacy at the end of weeks 1, 2, then every 4 weeks for 24 weeks. Biochemical and hematological profiles were checked initially fortnightly and then monthly for 24 weeks. Serum HCV RNA was done before treatment, at 24 weeks of treatment and at 24 weeks after the end of treatment. The primary end point was an end of treatment response and sustained virological response defined as, the absence of serum HCV RNA at the end of treatment and 24 weeks after completion of therapy. Secondary end point was normalization of the serum ALT concentration. All the record of the patients was kept in separate files for each patient at DHQ Hospital Dir (upper).

RESULTS

Three hundred and forty-seven patients with chronic hepatitis C were treated during the study period with 249 (71.75%) males and 98 (28.25%) females of adult age group. Five (1.57%) patients were lost to follow up and three (0.94%) patients left treatment because of adverse effects of drugs. A total of 339 patients finally completed the therapy. The serum HCV RNA became undetectable in 229 (67.5%) patients at end of 24 weeks (End Treatment Response) and 210 (61.94%) at 24 weeks after the completion of treatment (Sustained Virological Response)

Among 339 patients who completed the therapy 96 were female and 243 were male. Different characteristics of male and female patients are given in Table 1.

Normalization of ALT, end treatment response and sustained virological response in the male and female group is summarized below (Table 2).

The ALT decreased during treatment to normal values at 24 weeks in those patients who had lost HCV RNA after 24 weeks of treatment and few of the non-responders and it remained normal at 6 months after the end of the treatment.

Table 1: Different characteristics of male and female patients

Characteristics	Male	Female
Male/Female	243	96
Mean age (years) ± SD	42 ± 2	37 ± 3
Mean serum ALT (IU/L) ± SD	105 ± 10	101 ± 8
Mean Hb (gm/dl) ± SD	12.8 ± 0.3	12.0 ± 0.4
Presence of cirrhosis	Nil	Nil

Table 2: Treatment response and sustained virological response in male and female patients

Parameters	Male (n=243)	Female (n=96)	P-value
Normalization of ALT	170/243 (69.95%)	69/96 (71.87%)	< 0.05
End Treatment Response	163/243 (67.07%)	66/96 (68.75%)	< 0.05
Sustained Virological Response	150/243 (61.92%)	60/96 (62.50%)	< 0.05

(P-value of less than 0.05 was considered significant)

The hemoglobin decreased by an average 2gm/dl during treatment and became normal after the completion of treatment. Two patients had to be started on iron and hematonics because of decrease hemoglobin concentration of 3gm/dl. No other significant adverse effects were noted in our patients. In the rest of patients, the side effects were mostly influenza like symptoms, body aches and minor psychiatric reactions, which occurred in most of the patients and were managed conservatively.

DISCUSSION

Hepatitis C is an infectious disease affecting the liver, caused by hepatitis C virus[8]. Hepatitis C virus cause both acute and chronic hepatitis. Spontaneous viral clearance rates are highly variable and ranges between 10- 50 %[9], and most patients develop chronic hepatitis i.e. infection lasting more than 6 months[10-12]. Among those chronically infected 20-30 % will eventually develop cirrhosis and its sequelae over 10-20 years[13].

Chronic hepatitis C infection also increases the risk of hepatocellular carcinoma. It is estimated hat 2-6.7 % of all patients with hepatitis C induced cirrhosis will develop hepatocellular carcinoma over 10 years and the annual risk is 1-4 %.

Previously combination of conventional interferon and Ribavirin was used to treat chronic hepatitis C, but now pegylated interferon with Ribavirin is the recommended treatment. The goal of the treatment is sustained virological response (SVR) which is absence of HCV RNA from the serum six months after stopping the treatment.

The primary endpoint in this study was a sustained virological response (SVR). The SVR substantially reduces the rate of HCC[14], leads to progressive histological improvement[15], and improved quality of life[16]. The secondary endpoint was normalization of the serum ALT. The better Sustained virological response rate in our study as compared to international studies is probably due to genotype 2 and 3, which is common in our region[17-18]. The definite evidence is not available as genotyping was not performed in our study and most other studies from Pakistan due to financial constraints.

The good end of the treatment and sustained virological response in the female group is most likely due to the lesser mean age of the patients, good compliance with the therapy. The female group of patients was on average 4.9 years younger than male group.

ALT levels decreased during treatment and it became normal at 24 weeks in those patients who had lost HCV RNA after 24 weeks of treatment and it remained normal at the end of treatment. The negative PCR results 24 weeks after stopping treatment is the most reliable marker of long term SVR[19]. The monitoring of response to treatment is recommended with qualitative polymerase chain reaction (PCR), which is an important tool for detection of HCV RNA in hepatitis C Patients[20]. In our study, the overall response rate to conventional interferon and Ribavirin combination therapy is higher as compared to other international studies[21-25] however the end treatment and sustained virological response is almost similar to the published data from Pakistan[26,27]. Ashraf et al have reported 79 % of response rate at the end of 24 weeks[28]. A sustained virological response of 71.4% with combination therapy has been reported by Wazir et al[29]. As the response with conventional interferons and Ribavirin in genotypes other than 1 and 4 is excellent[30,31] and considering emerging data of equal response rates of conventional and pegylated interferons in genotypes 2 and 3 patients in Pakistan, the Pakistan Society of Gastroenterology and GI endoscopy and Pakistan society of Hepatology National Consensus Guidelines 2009 has recommended standard interferons and ribavirin as the first line of treatment for chronic hepatitis C genotype 2 and 3 patients in Pakistan[32].

CONCLUSION

Combination of conventional interferon and ribavirin has a high sustained virological response with fewer side effects in our study. In resource depleted countries like Pakistan, we recommend conventional interferon and ribavarin combination therapy instead of pegylated interferons and ribavirin, as the first line treatment for non affording chronic hepatitis C patients.

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CONTRIBUTORS

NI conceived the idea and planned the study. IA did the data collection and helped in the writeup of the study. Both the authors contributed significantly to the research that resulted in the submitted manuscript.