Original Article

Interferon treatment in Hepatitis C

Standard Interferon in the Treatment of Hepatitis C; Response Rate in Genotypes 2 and 3 from an Area in Azad Kashmir, Towards North of Pakistan

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ABSTRACT

Objective: To assess the response rate and side effect profile of combination therapy with standard interferon alpha 2a and ribavirin in patients with chronic hepatitis C, genotype 2 and 3.

Study Design: Observational study

Place and duration of Study: This study was conducted at Saleem Medical Complex and Maryam Maternity home, Kotli, Azad Kashmir from January 2012 to December 2012.

Materials and Methods: Both male and female patients above 20 years of age with chronic hepatitis C, living in district Kotli Azad Kashmir, not treated previously, were included in the study. Viral load and genotyping were determined before initiation of treatment. Therapy was given with conventional interferon alpha 2a, 3 Million international units subcutaneously on alternate days and ribavirin 400mg tablets orally daily, for 24 weeks. PCR was repeated at the end of treatment and six months later. Clinical and lab monitoring was done at regular intervals and side effect profile was recorded.

Results: Out of 150 patients, 30 (20%) were males and 120 (80%) were females. Most of the patients were between 20-50 years of age (83.99%). End of treatment response was 82% and sustained viral response was 65.33%. Fever was the most common side effect followed by flu like symptoms. All the patients completed the treatment without any dropout.

Conclusion: The study showed a good response rate to standard interferon plus low dose ribavirin against genotype 2 and 3, with a favorable side effect profile without any drop out, indicating that it is a suitable treatment option.

Key Words: hepatitis C; genotypes 2 & 3; interferon alpha 2a

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INTRODUCTION

Hepatitis C is highly prevalent throughout the world. According to WHO, more than 130 million people are infected worldwide and incidence of new cases is 3-4 million per year[1,2,3]. The high prevalence rates are found in Africa (5.3%), Eastern Mediterranean (4.6%) and western pacific (3.9%)[1]. It may be associated with liver cirrhosis in 5-20% of patients over a period of 20-25 years and 30% of them may develop end stage liver failure over a period of 10 years[4]. Of those with cirrhosis 30-50% may develop Hepatocellular carcinoma[2]. Other extra hepatic complications are mixed cryoglobulinaemia, non-Hodgkin lymphoma and membrano-prolifeartive glomerulonephritis[2,4]. Due to these serious complications, it becomes essential to treat the infected patients. If a sustained virological response (SVR) can be achieved with treatment, all the complications may be prevented and natural history of the disease may change[2]. Previously it was known as Non A, Non B hepatitis. In 1989 it was named as Hepatitis C virus[5,6]. Response to interferon alone was not very encouraging but combination therapy with interferon and ribavirin for 48 weeks increased the response rate significantly to 63-66% compared to 7-11% with interferon monotherapy[7,8,9,10,11]. Response rate improved further after the introduction of pegylated (peg) interferon. In Asians, improvement was better than Caucasians[2,12].

Treatment response depends on various variables including genotype, pre and post treatment viral load, serum ALT level, platelet count, body mass index (BMI), co infection with Hepatitis B, alcohol consumption and duration of therapy[4,13,14]. Current standard treatment of chronic hepatitis C is either standard interferon α 2a or 2b (3 million international units (MIU) subcutaneously (SC) three times weekly) or Peg-interferon along with ribavirin[15]. Peg interferon

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and ribavirin are more effective for genotype 1. But the results for genotype 2 and 3 with both types of interferon are almost similar so that for these genotypes standard interferon can be used instead of peg interferon[11]. It is a great advantage because former is much cheaper than the later. In developing countries like Pakistan, standard interferon α with ribavirin is still the mainstay of treatment especially in government funded treatment programmes for hepatitis B and C.

In Pakistan prevalence of Hep C is more than 3% and genotype 3a is more prevalent followed by 3b, 1a, 1b and 2a; type 4 is least common[3]. Success of treatment is usually judged by measuring viral load. If it is undetectable by a sensitive laboratory test i.e. PCR (Polymerase chain reaction) at the end of treatment and six months after completion of therapy, it is termed as end of treatment response (ETR) and sustained virological response (SVR) respectively[4]. Goal of treatment is to eradicate the infection which is considered to be achieved if a patient gets SVR[1,4]. For genotypes 2 and 3, treatment for 24 weeks is usually sufficient[1].

We have tried to determine the response rate to standard interferon α and ribavirin in our patients infected with genotypes 2 and 3. Response rate of this regimen can vary in different populations as is shown by the different response rates observed in local American whites and blacks[4]. This may be attributed to differences in the natural immunity against the infection. We wanted to observe the situation in the area under study and compare it with the results in other parts of the world. This may also be useful to rationalize the treatment of genotype 2 and 3 with standard interferon and ribavirin, a much cheaper option than peg interferon.

We also wanted to determine the tolerance of the patients to this regimen by studying its side effect profile and dropout rate from the treatment program.

MATERIALS AND METHODS

This was an observational study conducted at Saleem Medical Complex and Maryam Maternity home, Kotli, Azad Kashmir, from January 2012 to December 2012. It included a total of 150 patients of chronic hepatitis C, both males and females, aged 20 years and above. Those who had already received interferon and ribavirin therapy were not included. In patients of chronic hepatitis C, who were diagnosed with ELISA (Biocheck USA), both the quantitative and real time qualitative PCR were done on Rotor-Gene g6000 by using Qiagen Artus (Germany). In those with positive PCR results, genotyping was done by Ohno Multiplex PCR method. Only patients with genotype 2 and 3 were included in the study. Liver biopsy was not done. In patients included in the study, liver function tests, urea, creatinine, prothrombin time, serum albumin, blood sugar, full blood counts along with platelet counts and abdominal ultrasound were performed. Patients with decompensated cirrhosis, very low TLC (<2500/ml) and platelets (<140,000 /ml) were excluded from the study. Informed consent was taken from the patients before starting them on treatment. They were given interferon alpha-2A, 3 MIU subcutaneously on alternate days and Ribavirin in a fixed dose of 400mg twice daily. Treatment was continued for 24 weeks. Patients took oral treatment at home and injection interferon at health facility near their homes. They visited Saleem Medical complex initially fortnightly and later on monthly for their clinical assessment, complete blood picture, ALT and abdominal ultrasound. All the information was recorded and side effect profile was maintained. At the completion of therapy, PCR was done to detect ETR and again six months later after completion of therapy to document SVR. Data was analysed by simple mathematics calculating percentages and using Excel 2013.

RESULTS

Among a total of 150 patients, 30 (20%) were males and 120 (80%) were females. Most of the patients were between 20-49 years of age (83.99%) (Table 1). ETR was 82% (n=123) and overall SVR was found to be 65.33% (n=98). (Table 2) Out of 123 with ETR, 25 (20.33%) patients relapsed. From a total of 150 patients, 52(34.67%) could not achieve SVR (27 non-responders and 25 relapsed). (Table 2)

Table No.1: Age wise distribution of patients who were given treatment for hepatitis C

Age group (years)	Number of patients	percentage
20-29	38	25.33%
30-39	40	26.66%
40-49	48	32%
50-59	15	10%
60-69	8	5.33%
70 and above	1	0.66%
Total	150	100%

Table No.2: Frequency of patients with ETR and SVR

	Patients with positive response		Non responders/ relapsed		Total number
	Numbers	%age	Number	%age	
End of treatment response (ETR)	123	82	27	18	Total patients 150 (100%)
Sustained virological response (SVR) out of ETR	98	79.67	25	20.33	Total with ETR 123 (100%)
Overall SVR	98	65.33	52	34.67	150 (100%)

Fever was the most common adverse effect observed during therapy (50%; n=75). Flu like symptoms, headache and hair loss were other common treatment

related adverse effects (26.66%, 20% and 13.33% respectively). Anaemia and thrombocytopenia were observed in 10% subjects each (n=15 each) but they were not severe enough to warrant for the discontinuation of therapy. Rates of neuropsychiatric problems (depression and encephalopathy) were low. (Figure 1) There was no death and all the patients completed the treatment.

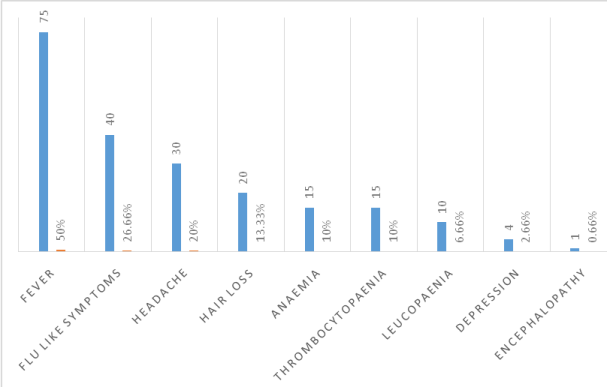

Figure No.1. Frequency of complications in patients receiving treatment for hepatitis C with standard interferon and ribavirin

Digits on top of the bars show the numbers and on side, the percentages

DISCUSSION

Treatment of Hepatitis C is important to prevent the morbidity and mortality and to control its spread in the community. From the earlier studies it was apparent that response rate to treatment was much higher for genotypes 2 and 3 as compared to genotype 1[16]. It was also documented through various studies that combination therapy with interferon and ribavirin was more effective and both new and relapsed cases gave better results with combination treatment than interferon alone[9,17]. In our study, ETR was 82% and SVR was 65.33%. This was quite an encouraging result, indicating a good response rate in the study population. In patients who develop SVR, natural history of the disease is altered and further progression either reverses or slows down with resultant decrease in complication rate[2]. An early viral response (EVR) (at least 2 log decrease in viral load by the end of 12 weeks of therapy) is a good predictor of SVR[11,13,17]. Rapid response at week 4 predicts achievement of SVR[18]. A viral load of <400,000 at the beginning of therapy was associated with good EVR[13].

Low platelet count (less than 140,000/ml) and high BMI (>30) are associated with relapse rate of 27.5%[4,13]. Poynard et al has included "age less than 40 years" and "female gender" as good prognostic indicators[10]. Alfredo Alberti mentioned that age alone could predict the disease outcome due to the presence of other metabolic co factors[19]. With increasing age, the chances of other co morbid conditions are higher while the chances of adherence to treatment are low[20]. Low albumin (less than 4 gram/dL) can also be taken as poor outcome predictor[21]. Presence of IL28BSNP (Interleukin 28B Single Nucleotide polymorphism) genotype confers a higher chance of achieving rapid virological response (RVR)[13,22]. Co infection with HIV, Hepatitis B and alcohol use further accelerate the chronic complications of hepatitis C[23].

In our study 27 (18%) were non responders. What should be the strategy for those who fail optimal treatment with interferon alpha and ribavirin is difficult to decide. They may be started on peg interferon and ribavirin but response rate is low (10%)[4]. Early disappearance of virus is associated with higher chances of achieving SVR. If there is low RVR and EVR, it is prudent to make early decisions about the continuation of treatment[7]. According to a study, 99% of those who attained SVR, maintained long term viral clearance for more than six year[24].

Patients in our study tolerated the therapy well and all of them remained adherent to the treatment till the end. A Japanese study showed that withdrawal rate from treatment was 13% in patients more than 65 and 7% in less than 65 years of age[25]. Interferon and ribavirin can lead to many haematological adverse effects[25,26,27].

CONCLUSION

Our study showed that response rate of patients with chronic hepatitis C, genotype 2 and 3, to standard interferon alpha and fixed low dose ribavirin was good. Side effect profile was favourable with minimum of adverse effects which did not lead to discontinuation of treatment. So conventional interferon which is cheaper, may be used instead of peg interferon in infection with genotypes 2 and 3. For non-responders and relapsed patients it is important to look for new, effective and cheap treatment options that are easily affordable by the poor local population.

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Conflict of Interest: The study has no conflict of interest to declare by any author.

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