ORIGINAL ARTICLE

RESPONSE TO DIFFERENT CONVENTIONAL INTERFERONS IN TREATMENT OF CHRONIC HEPATITIS C

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Background: Sustained virological response to interferon therapy is a great challenge for patients of chronic Hepatitis C. Over 20 brands of interferons are available in the local market with each claiming over 80% response and a wide variation in the cost thus creating confusion for treating physicians as to which drug should be selected. **Methods**: Chronic Hepatitis C patients attending outpatients department of Pakistan Medical Research Centre JPMC from January 1998–December 2010 were evaluated. Complete blood count, liver function tests, serum proteins, HCV-RNA were done in all cases before starting therapy. Side effects were also noted. **Results:** Total of 851 cases received interferon 3 MIU three times a week for 6 months. There were 638 (75%) males and 213 (25%) females, mean age was 36.1±10.4 years. All were HCV-RNA positive prior to treatment, at the end of 6 months 666 (78.3%) became negative while 185 (21.7%) were non-responders with positive HCV RNA. End of treatment response (ETR) showed 84.7% with Bioferon (Argentina), 83.8% Hebron (Cuba), 82.2% INF (Argentina), 82.1% Ceron (China), 81% Viteron (Korea), 80.7% Leveron (Argentina), 81.5% Hepaferon, 79.1% Anferon (China), 77.4% Intron (Belgium), 75% Green alpha (Korea), 74% Roferon (Switzerland), 67.3% Uniferon (Lithuania), and 68.4% with others. Post-treatment 211 cases were lost to follow-up. In remaining 358/640 (55.9%) negative for HCV-RNA, at six months follow up, whereas 98 (15.3%) relapsed. Sustained virological response (SVR) Ceron 68.2%, Hebron 66.3%, Bioferon 65.2%, Leveron 60.5%, Intron 60.3%, Viteron 57%, Anferon 53.3%, Green alpha, Roferon, Hepaferon, and others 50%, INF 48.5% and Uniferon 41.9%. Average cost of these interferons was Rs. 6,000/month, except Hepaferon 5,000/month, Roferon 10,600/month. **Conclusions:** ETR ranged from 74–84.7% and SVR 41.9% to 68.2% and >60% SVR was observed with Ceron, Hebron, Bioferon, Leveron, Intron and were cost effective.

Keywords: Conventional interferon, response, chronic Hepatitis C.

INTRODUCTION

Hepatitis C virus is a major public health problem and leading cause of chronic liver disease and hepatocellular carcinoma in Pakistan.[1,2] Overall prevalence of Hepatitis C in Pakistan is 4.9%. Type 3 is the predominant genotype in Pakistan,[3] which requires six months therapy[4]. Treatment strategy for chronic Hepatitis C is rapidly evolving, to achieve satisfactory response and long-term viral eradication. Interferon-alpha 2b was first introduced for the treatment of chronic Hepatitis C in 1986.[5] The sustained viral response rate with interferon monotherapy was only 10–20%.[6,7] Later it was found that adding ribavirin, which is an orally active synthetic guanosine analogue with antiviral and immunomodulatory property, could improve the outcome of interferon therapy[8,9] and this was a major breakthrough in chronic Hepatitis C treatment. Initial pilot studies showed combination therapy with interferon and ribavirin to be more effective than interferon alone.[10,11] Systemic review done by Kjaergard *et al* in 2001 for the Cochrane review included data of 6 trials in which patients received interferon monotherapy or interferon plus ribavirin therapy. The sustained virological response was 26% better in combination group as compared to monotherapy.[12] These remarkable results were more profound in patients with genotype 2 and 3.[13,14] Since then interferon plus ribavirin is the standard of care for the treatment of chronic Hepatitis C. Majority of our Pakistani population suffering from chronic Hepatitis C cannot afford pegylated interferon. Standard Interferon along with ribavirin remains the mainstay of therapy in our resource poor country. Previously published data shows treatment response of standard interferon as comparable to pegylated interferon.[15,16] In Pakistan more than twenty different brand of standard interferons are available, with different source of origin prices. Prescribing physician become confused as to which brand should be used? The only way to resolve this issue is to compare the results of available Interferons and scientifically document it. To achieve this goal the current study was undertaken to find out the sustained viriological response of the available brand of Interferons for the treatment of chronic Hepatitis C patients.

MATERIAL AND METHODS

Chronic Hepatitis C patients, treatment naive patients, treated with conventional interferon combination therapy and attending the outpatients department of Pakistan Medical Research Centre, Jinnah Postgraduate

Medical Centre, Karachi, from January 1998 till December 2010, were analysed.

Patients having anti-HCV, HCV-RNA positive for more than 6 months, along with deranged liver function tests and genotype/serotype 2 and 3 were included in the study after written informed consent. All cases with genotype/serotype 1, 4 and others, those previously treated with interferon, cirrhotics having signs of decompensation like oedema, ascites, oesophageal varices, coma and those with concurrent liver disease, human immune deficiency virus HIV/HBV, delta infection and incomplete follow up were all excluded from the study.

Baseline parameters like complete blood count (CBC), liver function tests, serum proteins with albumin globulin ratio, HCV-RNA (PCR), ultrasound abdomen were done and noted before starting therapy. Complete blood count and ALT were repeated every month and side effect profile was noted. HCV-RNA was repeated at the completion of therapy, i.e., 6 months and later 12 months to see the end treatment and sustained viriological response to treatment. All cases meeting the above mentioned criterion were included and treated with conventional interferon 3 MIU S/C three times per week plus 800–1200 mg ribavirin in divided dose according to weight (patients <70 Kg 800 mg and >70 Kg 1200 mg/day) for 6 months and those with complete follow up were analysed.

Response to interferon, especially with different brands of interferon, [Bioferon (Argentina), Hebron (Cuba), INF (Argentina), Ceron (China), Viteron (Korea), Leveron (Argentina), Hepaferon (China), Anferon (China), Intron (Belgium), Green alpha (Korea), Roferon (Switzerland), Uniferon (Lithuania) and others], the End Treatment Response (ETR) and sustained viral response (SVR) were analysed.

RESULTS

Out of a total of 851 cases included in the study, 638 (75%) were male and 213 (25%) were females. Mean age±SD was 36.1±10.4 years (age range10–80 years). Gender distribution amongst the different brands of interferon showed male predominance in all group of interferons but gender, age, platelet count and serum albumin (Table-1, 2) were not found to be statistically significant. Eight hundred and ten (95.2%) cases were genotype 3 and 41 (4.8%) were genotype 2. A total of 851 cases fulfilling the inclusion/exclusion criterion and were included in the study. Out of these 666 (78.3%) became HCV-RNA negative at completion of 6-month therapy (ETR) and 185 (21.7%) were non-responder as their HCV-RNA persisted to be positive even at the end of treatment. The individual response with different interferons, their country of origin and end treatment response is shown in Table-3.

Out of the 851 cases who completed six months therapy, 211 patients were lost to follow-up and were excluded from the final analysis of sustained virological response (SVR). In the remaining 640 cases who further came in the 6 months post-treatment follow up, HCV-RNA became negative in 358 (55.9%) cases, (SVR), whereas 98 (15.3%) cases relapsed. Sustained Virological Response with different interferons and their country of origin is given in Table-4. The average cost of all the interferons mentioned in this study is Rs. 6,000/month, except Hepaferon which cost Rs. 5,000/month and Roferon Rs. 10,500/month. Sustained virological response more than 60% was found with Ceron, Hebron, Bioferon, Leveron and Intron and were cost-effective.

Table-1: Gender distribution in different interferon groups

Treatment code	Total	Male		Female	
		No.	%	No.	%
Anferon	43	27	62.8	16	37.2
Uniferon	98	66	67.3	32	32.7
Hebron	111	82	73.9	29	26.1
Bioferon	59	47	79.7	12	20.3
INF	45	34	75.6	11	24.4
Viteron	137	111	81.0	26	19.0
Roferon	127	96	75.6	31	24.4
Hepaferon	27	18	66.7	9	33.3
Interon	84	68	81.0	16	19.0
Leveron	57	45	78.9	12	21.1
Ceron	28	22	78.6	6	21.4
Green Alpha	16	12	75.0	4	25.0
Intermax/Cell Aid/Pedferon	19	10	52.6	9	47.4
Total	851	638	75.0	213	25.0

Table-2: Baseline characteristics of different interferon groups Mean±SD

Treatment code	Subjects	Age (Year)	Platelets ($1000/mm^3$)	Albumin (g/dL)
Anferon	43	35.9±8.9	223±70	4.1±0.49
Uniferon	98	37.8±10.6	230±81	3.9±0.51
Hebron	111	36.0±9.6	232±74	4.0±0.45
Bioferon	59	34.8±9.9	207±68	4.0±0.37
INF	45	37.4±11.3	212±57	4.2±0.37
Viteron	137	33.1±9.8	222±82	4.1±0.44
Roferon	127	27.3±11.3	213± 65	4.0±0.49
Hepaferon	27	35.9±10.5	240±63	3.9±0.51
Interon	84	38.9±10.8	208±68	4.1±0.47
Leveron	57	37.7±10.8	210±77	4.0±0.40
Ceron	28	33.3±9.8	212±69	4.2±0.70
Green Alpha	16	30.9±6.1	214±54	4.1±0.31
Intermax/Cell Aid/Pedferon	19	35.8±9.7	227±41	4.2±0.56

Table-3: End Treatment Response at 6 months with brands of interferon

Treatment	No. of Subject	ETR at 6 months			
		Responder		Non responder	
		No.	%	No.	%
Anferon (China)	43	34	79.1	9	20.9
Uniferon (Lithuania)	98	66	67.3	32	32.7
Hebron (Cuba)	111	93	83.8	18	16.2
Bioferon (Argentina)	59	50	84.7	9	15.3
INF (Argentina)	45	37	82.2	8	17.8
Viteron (Korea)	137	111	81.0	26	19.0
Roferon (Switzerland)	127	94	74.0	33	26.0
Hepaferon (China)	27	22	81.5	5	18.5
Interon (Belgium)	84	65	77.4	19	22.6
Leveron (Argentina)	57	46	80.7	11	19.3
Ceron (china)	28	23	82.1	5	17.9
Green Alpha (Korea)	16	12	75.0	4	25.0
Intermax/Cell Aid/Pedferon	19	13	68.4	6	31.6
Total	851	666	78.3	185	21.7

Table-4: Sustained Viral Response with brands of interferon

Treatment code	Follow-up Available	Sustained Response		Relapse		Non responder	
		No.	%	No.	%	No.	%
Anferon (China)	30	16	53.3	5	16.7	9	30.0
Uniferon (Lithuania)	74	31	41.9	11	14.9	32	43.2
Hebron (Cuba)	86	57	66.3	11	12.8	18	20.9
Bioferon (Argentina)	46	30	65.2	7	15.2	9	19.6
INF (Argentina)	33	16	48.5	9	27.3	8	24.2
Viteron (Korea)	107	61	57.0	20	18.7	25	23.4
Roferon (Switzerland)	94	47	50.0	14	14.9	33	35.1
Hepaferon (China)	16	8	50.0	3	18.8	5	31.3
Interon (Belgium)	68	41	60.3	8	11.8	19	27.9
Leveron (Argentina)	38	23	60.5	4	10.5	11	28.9
Ceron (china)	22	15	68.2	2	9.1	5	22.7
Green Alpha (Korea)	12	6	50.0	2	16.7	4	33.3
Intermax/Cell id/Pedferon	14	7	50.0	1	7.1	6	42.9
Total	640	358	55.9	98	15.3	184	28.8

DISCUSSION

Combination of conventional or pegylated interferon along with Ribavirin is well-established regimen for the treatment of chronic Hepatitis C.[17] Conventional interferon combination therapy is being widely used for the treatment of chronic Hepatitis C, for two reasons: firstly as most predominant genotype in Pakistan is 3, which shows good result with conventional interferon, and secondly due to financial reasons. The cost difference between pegylated and conventional interferon is critical in a country where the average person earns 650 dollars/year and where there is no health insurance system. Based on these facts Pakistan Society of Gastroenterology has recommended conventional interferon and ribavirin as first-line of therapy for chronic Hepatitis C naïve patients.[18] So far conventional Interferons are being used to treat majority of the cases of chronic Hepatitis C all over the country, and more so in the public sector hospitals because of the very low paying capacity of the patients coming to these hospitals. It is more than a decade conventional Interferons are being used with different brand names of different source of origin. Hardly any comparative data is available regarding the efficacy and safety of these preparations. Limitation of this study is that not all groups of patients are equal in number; however an effort has been made to compare them as far as possible. Male predominance in each group of patients is quite evident. Over all 75% of the patients are male and only 25% of cases are female in this study, which is the general trend in our country.

The ETR in this study ranged from 74–84.7% with different interferons which shows that all of these interferons are quite effective in lowering down the viral load to such an extent that the PCR has become below the detection limit, after six months of interferon therapy in 78% of patients. The difference in the response rate though with individual Interferons is statistically not significant. However the actual response with interferon therapy should be judged by the sustained virological response, i.e., ALT levels and PCR six months after the cessation of therapy. The overall sustained virological response in this study is 55.9%, which range from 41.9% to 68.2% with different interferons. Since the number of patients in each group is not uniform, the comparative efficacy in terms of ETR or SVR is difficult to commit. However the difference in the sustained virological response with individual Interferons was significantly better observed with Hebron, Bioferon, and Viteron ($p<0.05$), and more than 60% sustained virological response was found with Ceron, Hebron, Bioferon, Leveron and Intron and are cost effective. Further studies are required to find out ETR and SVR in the similar fashion with equal distribution of patients in each group and with matching demographic criteria.

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