ORIGINAL ARTICLE

Tolerability Profile and Therapeutic Responses of Unipeg® plus Ribavirin in Patients with Untreated Chronic HCV Genotype 2 or 3 Infection

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ABSTRACT

Aim: To investigate the tolerability potential and therapeutic feedback of Unipeg® plus Ribavirin in untreated patients of chronic hepatitis C disease

Methods: A non randomized prospective clinical trial was conducted on ninety two patients of chronic hepatitis C with genotype 2 and 3 who were never treated with any antiviral based therapy previously. These patients were prescribed Unipeg® and Ribavarin at a dose of 180µg/week & 1000-1200/day respectively as a combination regime for a period of 24 weeks. Different virological as well as treatment responses were observed at specific intervals of time while safety profile of treatment regime were noted by both general physical as well as complete blood examination

Results: All patients completed the study with mean age of 36.12+10.79 years in which two third was male. A significant changes were seen in hematological parameters in terms of mean hemoglobin and WBC count which decreased in a linear fashion from start to end of treatment with p-values <0.001 and <0.001 respectively. There was no significant effect of antiviral regime on platelets counts (p-value 0.90). The neutrophil count decreased at 4th week while increased at 12th and 24th week as compared to baseline value (p-value <0.02).

Conclusion: The therapeutic responses and safety profile of UNIPEG® and ribavirin combination has similar outcome to most others brand available (PEG-INF α-2a) in the market.

Keywords: Unipeg®, Hepatitis C, Ribavirin

INTRODUCTION

Chronic hepatitis C is a silent killer which affects around 3% of population globally[1]. Patients with chronic hepatitis C infection may be asymptomatic for a numbers of years but it can progress to chronic liver disease to liver fibrosis & cirrhosis while hepatocellular cancer and hepatic failure are two worst complications of HCV infection. It is one of the leading cause of liver transplantation in developing countries[2]. The clinical as well as economical burden of HCV is on the rise in Pakistan because of multiple risk factors. About 2.5 to 4.8% population of Pakistan is affected by this virus and this number will definitely increase if preventive measures should not be undertaken[3]. The treatment options of HCV infection also progresses with time to time as Interferon plus ribavirin once considered being the standard treatment, were then replaced by Pegylated interferon and now by direct acting antiviral drugs. However pegylated interferon has numerous advantages because of more efficacy, few adverse effects, short duration of treatment and better pt's compliance as compared to standard interferons[4,5,6].

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In order to improve the efficacy of standard interferon's, these were conjugated with various polyethylene glycol (PEG) chain of different molecular weights. This property results in slow clearance and enhances its antiviral action by inhibiting viral replication for a longer period of time than standard interferons. Moreover due to long duration of action there dose are once a week with few adverse effects than standard interferons[7,8,9,10].

Unipeg® a branded pegylated interferon, conjugated with 20 KDa (Kilo Dalton) chain of PEG interferon produced biosynthetically by inserting a cloned human leukocyte interferon gene into Hansenula Polymorpha through DNA recombinant technology. Seeing this unique chemical modification of Unipeg® there was strong need to investigate its various therapeutic responses and safety profile in Pakistani population. So far only two clinical trials were conducted on healthy volunteers. Therefore we investigated the combined effect of Unipeg® and ribavirin in chronic hepatitis C patients with genotype 2 & 3 in terms of safety profile and treatment responses[10,11].

MATERIALS AND METHODS

A prospective non randomized clinical trial was conducted on ninety two patients of chronic hepatitis

C at medical outdoor unit of Sheikh Zayed Medical/Hospital Rahim Yar Khan for a period of one year (March 2015 to March 2017). On the basis of inclusion criteria, a total of 92 patients of both sexes aged 20-56 years who were anti HCV positive having genotype 2 & 3 with viral load were enrolled in this clinical trial. These patients were never treated with any antiviral based regime previously. Exclusion criteria was patients with genotype other than 2 & 3, concurrent hepatitis B infection, Fatty liver disease (alcoholic & non alcoholic), liver cirrhosis, hepatocellular cancer, metabolic syndrome, diabetes mellitus, HIV positive, low platelets (<50,000/ mm^3) and absolute neutrophil (< 30%) counts. A written informed consent was got from all participants while ethical permission was taken from institutional review board (IRB) before start of study.

Drugs Specifications: All patients were given a combination regime of injection pegylated interferon (Unipeg® containing 20kDa-INF-α-2a of gets Pharmaceutical company) subcutaneously at a dose of 180µg/week and oral Ribavirin at a dose of 1000-1200/day based upon body weight for a period of 24 weeks.

Response to treatment and safety evaluation: A fasting blood sample of 3 ml were drawn from antecubital vein to analyze complete blood examination , serum sugar and different virological responses (early virological response & rapid virological response) as well as end treatment responses at 0, 4, 12 and 24 weeks. Complete blood examination including hemoglobin, platelets counts, TLC and DLC counts were estimated by automated hematology analyzer SysmexKX-21 while PCR were analyzed by amplifying the core region of HCV through RT-PCR technique. Early and rapid virological response was defined as qualitative non detection of HCV RNA level at 4^{th} and 12^{th} week of combination therapy. On the other hand end treatment response as is defined as qualitative non detection of HCV RNA level at 24 week of treatment. In addition detailed medical history and general physical examination were undertaken to note any ontowards effects of therapy.

All clinical as well as laboratory results were analyzed using ANOVA test at different interval of time in which F-value & P-Value was determined .Adverse effects of treatment were calculated as frequency and percentage.

RESULTS

All patients completed the study with mean age of 36.12+10.79 years in which two third was male. There were 18 (19.6%) patients with genotype 2 and 74 (80.4%) with genotype 4 (table 1) .A significant changes were seen in hematological parameters in terms of mean hemoglobin and WBC count which decreased in a linear fashion from start to end of treatment with p-values <0.001 and <0.001 respectively. There was no significant effect of antiviral regime on platelets counts (p-value 0.90). The neutrophil count decreased at 4^{th} week while increased at 12^{th} and 24^{th} week as compared to baseline value (p-value <0.02) table 2. Headache and fever were the two most reported adverse effects during combination therapy followed by fatigue, anxiety, depression and diarrhea (table 3). Overall efficacy of unipeg in terms of early virological response, rapid Virological response and end-of-treatment response was 85 (92.4%), 39 (42.5%) and 62 (67.4%) respectively (table 4).

Table 1: Baseline Characteristics of Patients

Name of Variable	**Value**
Age	36.12+10.79
Male/Female Gender	56 (60.9)/36 (39.1)
BMI	23.16+4.11
Obese	5 (5.4)
Hypertension	3 (3.3)
HCV Genotypes	
Genotype 2	18 (19.6)
Genotype 3	74 (80.4)
Baseline Hemodynamic Characteristics	
Pulse Rate	81.70+6.13
Respiration Rate	20.63+1.30
Systolic Blood Pressure	120.0+8.77
Diastolic Blood Pressure	76.73+6.30
Baseline Hematologic Characteristics	
Hemoglobin	12.66+1.71
WBC Count	5971.30+18993.03
Platelet Count	183966.30+51544.23
Neutrophils	60.85+8.92

Table 2. Hematologic Parameters (Comparisons).

	Baseline	**At 4 weeks of treatment**	**At 12 weeks of treatment**	**At 24 weeks of treatment**	**F-value**	**P-value**
Hemoglobin	12.66+1.71	11.82+1.86	11.40+1.98	10.97+1.42	37.83	<0.001
WBC Count	5971+18993.03	5044+1379	4753+1341	4654+1379	14.64	<0.001
Platelet Count	183966+51544	192673+167269	181652+138127	179541+141545	0.19	0.90
Neutrophils	60.85+8.92	58.81+8.49	61.14+8.2	61.58+7.70	3.08	0.02

Table 3: Adverse effects (Incidence) during treatment.

Name of Variable	Frequency	%age
Adverse Events at 4th week of Treatment		
Fever	53	57.6
Headache	55	59.8
Mild Anxiety	20	23.3
Depression	25	21.7
Fatigue	32	34.8
Diarrhea	7	7.6
Adverse Events at 12th week of Treatment		
Fever	52	56.5
Headache	58	63.0
Mild Anxiety	17	18.5
Depression	27	29.3
Fatigue	34	37.0
Diarrhea	10	10.9
Adverse Events at 24th week of Treatment		
Fever	53	57.6
Headache	55	59.8
Mild Anxiety	19	20.7
Depression	26	28.3
Fatigue	33	35.8
Diarrhea	5	5.4

Table 4: Unipeg Treatment Outcomes .

Outcome	Frequency	%age
Rapid Virological Response	39	42.5
Early Virological Response	62	67.4
End-of-treatment Response	85	92.4

DISCUSSION

The treatment of chronic hepatitis C infection advances with the passage of time. First interferon and ribavirin were considered to be the treatment of choice for chronic HCV patients. In early 2000 pegylated interferon (α-2a or 2b) came in the market with improved efficacy, less adverse effects and better patient's compliance. These pegylated infernos now replaced by oral direct acting antiviral agents (DAAs) with better safety profile in comparison with older regimes. In spite of too many advances, pegylated interferon and ribavirin still the treatment of choice in chronic HCV patients with genotype 2, 3 and 4(4). Studies have shown that PEG-INF α-2a is better than α-2b in terms of various treatment response and safety profile (12, 13). So in this study we investigate the different virological and treatment response as well as safety and tolerability profile of PEG-INF α-2a (brand Unipeg®) and compared it with our previous published studies.

In our study after treatment with PEG-INF α-2a early virological response was 67.5% which was comparable with other studies (69-83%) in chronic HCV patients with genotype 2 and 3[12,14]. A study conducted by Fried et al revealed different end treatment response after treatment with PEG-INF α-2a and interferon α-2b with ribavirin combination which were 69% and 52% respectively[14]. Similar type of work was conducted by Ascione et al which showed that end treatment response was 83.8% by using PEG-INF α-2a while it was 64.4% by using PEG-INF α-2b along with ribavirin as combination therapy[12]. In these studies researcher used Pegasys as 40KD conjugated Interferon α-2a(Hoffmann–LaRoche) while we used Unipeg® as 20KD conjugated Interferon α-2a (Gets Pharma)

Regarding hematological parameters after treatment with Unipeg (PEG-INF α-2a), our study showed similar results to various other studies which used pegasys (PEG-INF α-2a), such as decrease in mean hemoglobin level, no effect on platelets count, first little decrease in neutrophil count at 4th week but then increased above the baseline throughout the study period (12, 14,15). .

In our study more than 50% of patients complaint of headache and fever followed by fatigue as an adverse effects. Other studies reported too as headache and fever were the major adverse effect. In comparison to our study the percentage of fatigue was quite high using pegasys in both adults (54%) and children (34%).In our study we used Unipeg, so fatigue was 34-37% which was quite less than Pegasys(14, 16).

So in this study unipeg which is 20 kda almost showed comparable results in terms of early virological response, rapid virological response, end treatment response, safety and tolerability profile to pegasys which is 40 kda.

CONCLUSION

The therapeutic responses and safety profile of UNIPEG® and ribavirin combination has similar outcome to most others brand available (PEG-INF α-2a) in the market.

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