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Comparative safety and efficacy of conventional interferon versus pegylated-interferon based therapy for HCV: A retrospective cohort study from Gujranwala, Pakistan

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Abstract: Numerous studies on risk factors, clinical presentation and treatment of hepatitis C are known to the world. However, no data is available about the safety and efficacy of anti-hepatitis C therapy among the patients of Gujranwala, Pakistan. This retrospective study compared two dosage forms of interferon; conventional interferon (IR) and Pegylated interferon (PIR) in 370 Hepatitis C patients selected through non probability convenient sampling technique. Clinical data were collected related to therapy outcomes at the start of therapy, after each follow up and at the end of therapy. The study indicated that HCV 3 was the most prevalent genotype of hepatitis C. Main side effects associated with therapies were pain at injection site (PIR; 49%, IR; 48%), inflammation at injection site (PIR; 34%, IR; 48%), fever (PIR; 56.12%, IR; 61.5%), myalgia (PIR; 24.5%,IR; 22.99%), malaise (PIR; 7.14%, IR; 5.75%), anorexia (PIR; 46%, IR; 39%), vomiting (PIR; 43%, IR; 41%), irritability (PIR; 4%, IR; 11.5%) and impaired concentration (PIR; 13%, IR; 21). The sustained viral response rate was significantly better in PIR group as compared to IR group (PIR; 80.61%, IR; 66.67%). In conclusion Pegylated interferon based therapy showed better clinical response with less adverse events as compared to conventional interferon based therapy. However, there is dire need to shift from these intravenous dosage forms to relatively new oral dosage forms for the treatment of hepatitis C to further improve clinical outcome and minimize the risks of adverse events.

Keywords: Conventional interferon, genotype, pegylated interferon, polymerase chain reaction, sustained virological response

INTRODUCTION

Hepatitis C is caused by Flaviviridae family and genus Hepacivirus, together with flaviviruses and pestiviruses leading to chronic liver disease, cirrhosis, hepato-cellular carcinoma (HCC) and transplantation of liver infecting approximately 170 million people around the globe (Hanafiah *et al*., 2013). Acute symptoms resolve in most of the patients, however, persistently raised ALT and HCV RNA level indicate chronic hepatitis C. This progression is influenced by many factors like alcohol consumption, age, degree of inflammation, stage of fibrosis, HIV and HBV co-infection and related co-morbidities (Chen and Morgan, 2006). Symptoms of chronic hepatitis are usually nonspecific and range from malaise to fatigue, pain in right upper quadrant, dark urination, itching, and cryoglobulinaemia, glomerulo-nephritis and skin rashes. However, slow progression results in end stage liver disease characterized by jaundice, weakness, fluid retention, upper intestinal hemorrhage, muscle wasting and gastrointestinal bleeding and risk of developing HCC (Hoofnagle, 1997). Polymerase chain reaction (PCR) is widely used to detect possible viraemia in patients with acute HCV infection with serological assay i.e anti HCV IgG assay for disease staging (Orland *et al*., 2001), and molecular assay to detect viral nucleic acid (Ghany *et al*., 2009), liver biopsy (Mutimer *et al*., 2014) and other novel methods (Kamili *et al*., 2012).

The control of hepatitis C by interferon therapy is recognised even before the viral cause was discovered, responsible for the normalization of alanine aminotransferase level (ALT). The first case of HCV infection successfully treated with interferon-α (INF) was reported in 1989, but high rate of relapses was major indication for the re-treatment with minimum success rate (Davis *et al*., 1989). Different interferons were used with similar efficacy. However, with the introduction of combination therapy with Ribavirin showed improvement in the disease progression (Lauer and Walker, 2001). Interferon therapy response is measured in terms of biochemical response i.e. measurement of improved aminotransferases, but now a days, detection of viral RNA, measured as sustained virological response (SVR). Patients with SVR have higher chances of improved biochemical, virological and histological response (Lauer and Walker, 2001). Later on, Pegylated interferon (2a & 2b) were used with Ribavirin in the treatment of hepatitis C patients to maximize the response rate (Foster, 2004). It increases the SVR from 54% to 63% as compared to 40%

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with combination therapy of IFN and Ribavirin. Conventional interferon is not suitable for non-responding patients; these patients respond well to peg-interferon and Ribavirin. Interferon treatment during acute stage has less progression from acute to chronic,while in chronic cases it is twice effective than INF in achieving SVR and relapse rate reduction by the continuation of interferon-2b and Ribavirin even after completing therapy (Zeuzem *et al*., 2000). This study was aimed to compare clinical efficacy and safety of both conventional and Pegylated interferon among hepatitis C patients of Gujranwala, Pakistan.

MATERIALS AND METHODS

Study method

A comprehensive instrument was designed to cater all the necessary objectives of the study. The hospital information system (HIS) was utilized to retrieve pertinent patient's medical records, demographics, disease history, symptoms and possible drug related side effects. Primary end point, HCV RNA was checked at the start as a baseline and then after 6 months of treatment for both conventional interferon and Pegylated interferon with Ribavirin. Laboratory values ALT, AST, Hb levels, TLC, platelets, lymphocytes were examined every month. Patients were examined regularly for therapeutic response after 4, 12 and 24 weeks. Polymerase chain reaction (PCR) was performed for HCV before starting therapy, after 12 weeks and at the completion of the treatment to check the end treatment response (ETR). Main indicators of treatment efficacy was the achievement of sustained virological response (SVR), undetectable level of HCV RNA (<50 IU/ml) with a detection limit of <15 IU/ml at the completion of the treatment till 6 months and a positive biochemical response i.e. serum ALT normalization.

Study center

Hepatitis C patients registered at two major health care facilities of the city, Chaudhary hospital satellite town, Gujranwala and District headquarter teaching hospital (DHQ/Teaching hospital), Gujranwala. These two hospitals are major hospitals; receiving hepatitis C referred patients from all over the district.

Study design

It is a retrospective cohort study of 6 months duration to assess the safety and effectiveness of interferon in hepatitis C patients of Gujranwala, using either conventional interferon or Pegylated interferon. The hospital information system (HIS) was utilized to retrieve pertinent patient's medical records.

Inclusion criteria

Eligible candidates for the study were either previously treated/untreated patients of hepatitis C (HCV positive) both by PCR (qualitative or quantitative) - irrespective of the genotype, gender, age and social status.

Exclusion criteria

Patients who failed to complete their therapy and using regimens other than combination of Ribavirin and conventional/Pegylated interferon were excluded from the study.

Study approval

The ethical approval of the study was taken from clinical research committee, Punjab University College of Pharmacy, University of the Punjab (ECCR/UCP/08/2015). The hospital administration allowed collecting this retrospective data from patient records from May 2012 to June 2015.

Sample size

A total 370 patients were included for this study. Out of 370 patients, 174 patients were undergoing treatment with interferon α-2a or 2b and Ribavirin while 196 patients were taking Pegylated interferon and Ribavirin.

STATISTICAL ANALYSIS

Data was analyzed using statistical package for the social sciences (SPSS) IBM, version 21 to relate the different side effects and symptoms of these two treatment groups. Pearson's Chi-Square Test/Chi-Square Goodness-of-Fit was applied to calculate *p*-value, odd ratio (OR) and confidence interval (95%). Graphs and tables were drawn accordingly by Graph pad (prism 5) of treatment groups.

RESULTS

Patient characteristics

Patient's basic demographic data and clinical presentation is summarized in table 1. In both categories, differences in mean frequency distribution were observed regarding age (PIR; 39.88 yrs, IR; 40.50 yrs), most patients were <45 years of age (PIR; 69.39%, IR; 64.94%), gender (male, PIR; 49%, IR; 55%), (female, PIR; 51%, IR; 45%) and marital status (married, PIR; 87%, IR; 84%). In PIR arm, patients seem to be more literate 43.88% compared to IR 39.08%. Risk factors (source) of infection by HCV were different but dental procedure (PIR; 46%, IR; 49%), Surgery (PIR; 38%, IR; 24%), Shaving outside (PIR; 27%, IR: 28%), dispensers (PIR; 23%, IR; 45%) and blood transfusion (PIR; 21%, IR; 18%) effect significantly. Other factors such as personal contact, organ transplantation and job related dealing with blood was also affecting the patients. Viral genotypes of the affected patients were assessed by PCR before initiating therapy in both the groups. Genotype 3 was the most prevalent as shown in fig 1, in both treatment arms (PIR; 86.22%, IR; 92.5%) followed by genotype 1 & 2. About 2 (1%) patients from PIR group, 6(3%) from IR group were infected with HBV. Patients belonging to the PIR arm have wider family history of HCV infection as compared to conventional IR group (PIR; 11.7%, IR; 6.90%).

Table 1: Basic demographics and disease history of patients underwent interferon and Ribavirin combination therapy for HCV

Parameter	Peg- interferon with Ribavirin N=196	Interferon with Ribavirin N=174
Age (yrs)	39.88	40.50
<45	136 (69.39%)	113 (64.94%)
>45	60 (30.61%)	61 (35.06%)
Male	97 (49%)	96 (55%)
Female	99 (51%)	78 (45%)
Weight (kg)	64.59	67.38
<60 kg	80 (40.82%)	65 (37.36%)
>60 kg	116 (59.18%)	109 (62.64%)
Education		
literate	86 (43.88%)	68 (39.08%)
Illiterate	110 (56.12%)	106 (60.92%)
Marital status		
Single	25 (13%)	28 (16%)
Married	171 (87%)	146 (84%)
Risk factor of disease (source)		
Blood transfusion	42 (21%)	32 (18%)
Dispensers	45 (23%)	78 (45%)
Organ transplant	1 (0.5%)	0
Personal contact	13 (7%)	3 (2%)
Job deal with blood	3 (2%)	3 (2%)
Shaving outside	53 (27%)	48 (28%)
Dental procedure	91 (46%)	86 (49%)
Surgery in last year	74 (38%)	42 (24%)
Family History	23 (11.7%)	12 (6.90%)
Genotype		
1,1b	22 (11.23%)	5 (3%)
2,2a	5 (2.55%)	8 (4.5%)
3,3a,3b	169 (86.22%)	161 (92.5%)
Super-infection of HBV	2 (1%)	6 (3%)
Baseline laboratory values		
HCV RNA Load		
Mean copies/ml $\times 10^6$	1.3 ± 3.4	3.4 ± 8.7
$< 2 \times 10^6$ copies/ml	173 (88.27%)	120 (68.97%)
$>2 \times 10^6$ copies/ml	23 (11.73%)	54 (31.03%)
ALT	77.56 ± 53.64	97.24 ± 67.04
AST	71.88 ± 44.67	74.39 ± 52.92
Hb	13.34 ± 1.85	16.40 ± 30.17
History		
Decompensated cirrhosis	16 (8.16%)	9 (5.17%)
Hepato-cellular damage	51 (26.02%)	25 (14.36%)
Fibrosis	43 (21.93%)	25 (14.36%)
Co-morbidities		
Abdominal pain	30 (15%)	18 (10%)
Genitourinary Problem	2 (1%)	4 (2%)
Respiratory tract infections	18 (9%)	8 (5%)
Hypertension	33 (17%)	32 (18%)
Skin disorder	8 (4%)	6 (3%)
Diabetes mellitus	17 (9%)	8 (5%)
Joint disorders	24 (12%)	17 (10%)

Hepatitis C viral load at the start of treatment as a base line value was (mean copies/ml $\times 10^6$, PIR; 1.3 ± 3.4, IR; 3.4 ± 8.7) and a low level of viral load (< 2 $\times 10^6$ copies/ml, PIR; 88.27%, IR; 68.97%) and a higher load (>2 $\times 10^6$ copies/ml, PIR; 11.73%, IR; 31.03%). Mean (SD) ALT and AST before treatment was determined by liver function test (LFTs) as (PIR; 77.56 ± 53.64, IR; 97.24 ± 67.04 and (PIR; 71.88 ± 44.67, IR; 74.39 ± 52.92) respectively. Both parameters were higher in conventional IR arm. Disease history showed that PIR arm has more decompensated cirrhosis (PIR; 8.16%. IR; 5.17%), hepato-cellular damage (PIR; 26.02%, IR; 14.36%) and fibrosis (PIR; 21.93, IR; 14.36%) compared to conventional IR group before treatment. According to co-morbidities data, hypertension was most prevalent both the groups, (PIR; 17%, IR; 18%) followed by abdominal pain (PIR; 15%, IR; 10%) and joint disorder (PIR; 12%, IR; 10%).

Treatment safety and efficacy

Side effect profile was similar with both the therapeutic arms. However, pain at injection site was more after PIR treatment (PIR; 49%, IR; 48%) as compared to IR treated patients, conversely, a marked *inflammation at injection site was observed (PIR; 34%, IR; 48%). General side effects include fever (PIR; 56.12%, IR; 61.5%) with *p*-value (0.295), myalgia (PIR; 24.5%, IR; 22.99%) having *p*-value (0.735), was lower in PIR arm compared to IR arm. While, malaise (PIR; 7.14%, IR; 5.75%) and headache (PIR; 12.25%, IR; 9.77%) having *p*-value (0.449) observed more in PIR than IR. Furthermore, frequency of GIT affects anorexia (PIR; 46%, IR; 39%) with *p*-value (0.124) and vomiting (PIR; 43%, IR; 41%) having *p*-value (0.699) were slightly increased in PIR treated group compared to IR treatment arm, as shown in table 2. On the other side, **mouth sores, a side effect of interferon therapy, was predominantly observed in IR treatment arm (PIR; 7%, IR; 17%). Significant psychiatric side effects include, depression (PIR; 14.29%, IR; 16.67%), *irritability (PIR; 4%, IR; 11.5%) and *impaired concentration (PIR; 13%, IR; 21) with *p*-value (0.029) more commonly observed with IR regimen but **insomnia was more frequently associated (PIR; 69%, IR; 50.58%) with PIR arm as shown in table. Hematological symptoms i.e anemia (PIR; 38%, IR; 49%), *thrombocytopenia (PIR; 6%, IR; 14%) were significantly present with *p*-value of 0.024 & 0.013 respectively. Dermatological side effects such as rashes (PIR; 20%, IR; 24%), **pruritus (PIR; 38%, IR; 16%), and **erythema at injection site were present highly significant shown in fig 2.

Treatment outcomes assess the treatment efficacy for both groups as shown in table 4. This table compares the response of different parameters of both the groups in terms of RNA detected after 6 months of completion of therapy (SVR). Sustained virological response (SVR) was determined 6 months later after completion of therapy. SVR achievement was found to be higher in PIR treated patients as compared to IR group (PIR; 80.60%, IR; 66.67%). Patients having RNA detected were more in IR and Ribavirin combination arm as patients of age <45 years (PIR; 14.70, IR; 25.66%) were less as compared to age >45 years (PIR; 30%, IR; 47.54%). Age of >45 years have more patients with RNA detected in both inter and intra arms. Detection of RNA was more observed in females (PIR; 25.25%, IR; 34.62%) as compared to males (PIR; 13.40%, IR; 32.30%). Illiterate people (PIR; 16.36%, IR; 34.91%) have more RNA detected as compared to literate (PIR; 23.26%, IR; 30.88%) in both arms. Married people (PIR; 20.5%, IR; 34.25%) have more RNA as compared to single (PIR; 12%, IR; 28.57%). Comparison of SVR with respect to genotype shows that genotype 3 was more prevalent in our enrolled patients. Genotype 1, 1b (PIR; 4.55%, IR; 60%) and genotype 3, 3a, 3b (PIR; 21.30%, IR; 33.54%) have more RNA detected in conventional as compared to PIR arm while genotype 2, 2a (PIR; 20%, IR; 12.5%) was found more in PIR than the IR arm.

Viral load affects the SVR as the higher viral load >2×10^6 (PIR; 17.34%, IR; 27.5%) has more RNA detected as compared to low viral load <2×10^6 (PIR; 34.78%, IR; 46.30%) in both arms. Cirrhosis, hepatic damage and fibrosis also have impact on SVR as it is higher in these patients in both arms. Patients having cirrhosis were (PIR; 31.25%, IR; 44.44%) while those having no cirrhosis were detected with RNA as (PIR; 18.33%, IR; 32.73%). Those having hepatic damage were detected with RNA (PIR; 32.61%, IR; 48%) while with no hepatic damage as (PIR; 15.33%, IR; 30.87%) higher in IR than PIR. Patients with fibrosis had RNA (PIR; 25.64%, IR; 25.64%) and those without fibrosis had RNA (PIR; 17.33%, IR; 30.87%).

In both groups of patients treated with these two regimens, normalization of histological response was observed during course of therapy, irrespective of the achievement of SVR and at the termination of the therapy. Overall patient response/outcome was assessed to be more improved with PIR as compared to IR (PIR; 87.75%, IR; 74.71%). Achievement of SVR was irrespective of age, gender, and mean body weight. Response rate found to be high with PIR treated group than IR. HCV RNA was not detected in 158/196 patients of PIR group and 116/174 patients using IR. Bio-chemical response such as normalization of ALT (PIR; 68.13%: IR; 33.98%) and AST improvement was observed (PIR; 52.44%: IR; 44.40%). Mean ALT & AST values (PIR; 35.33 ± 21.02, IR; 33.04 ±21.97) and (PIR; 37.69 ± 23.29, IR; 33.03 ± 29.11) with percentage reduction of (PIR; 54.45%, IR; 66.02%) and (PIR; 47.57%, IR; 55.61%) respectively. Percentage reduction was more in PIR as compared to IR. Reduction in hemoglobin percentage was more in the conventional than peg-interferon (PIR; 8.85%, IR; 31.71%).

Table 2: Side effects observed in patients undergoing interferon therapy in HCV patients

Side Effects	Peg-interferon with Ribavirin N=196	Interferon with Ribavirin N=174	OR (95% CI)	*P*-value
Injection site reactions				
Inflammation	67 (34%)	84 (48%)	0.556 (0.366-0.846)	*0.006
Pus formation	09 (4.59%)	02 (1.15%)	4.139 (0.882-19.425)	0.052
Severe pain	96 (49%)	84 (48%)	1.029 (0.684-1.547)	0.892
None	24 (12%)	04 (2%)	5.930 (2.015-17.454)	**0.000
General				
Fever	110 (56.12%)	107 (61.50%)	0.801 (0.528-1.214)	0.295
Malaise	14 (7.14%)	10 (5.75%)	1.262 (0.545-2.918)	0.586
Myalgia	48 (24.50%)	40 (22.99%)	1.086 (0.672-1.756)	0.735
Headache	24 (12.25%)	17 (9.77%)	1.289 (0.667-2.488)	0.449
Gastrointestinal symptoms				
Anorexia	91 (46%)	67 (39%)	1.384 (0.914-2.096)	0.124
Vomiting	85 (43%)	72 (41%)	1.085 (0.718-1.640)	0.699
Hepatic-Decompensation	06 (3%)	06 (3%)	0.884 (0.280-2.794)	0.834
Oral sores	14 (7%)	29 (17%)	0.385 (0.196-0.755)	**0.004
Psychiatric Symptoms				
Depression	28 (14.29%)	29 (16.67%)	0.833 (0.474-1.466)	0.527
Insomnia	135 (69%)	88 (50.58%)	2.163 (1.415-3.305)	**0.000
Irritability	08 (4%)	20 (11.5%)	0.328 (0.140-0.764)	*0.007
Impaired concentration	25 (13%)	37 (21%)	0.541 (0.311-0.943)	*0.029
Hematological symptoms				
Anemia	74 (38%)	86 (49%)	0.621 (0.410-0.939)	*0.024
Thrombocytopenia	12 (6%)	24 (14%)	0.408 (0.197-0.842)	*0.013
Not Specific	110 (56%)	64 (37%)	2.198 (1.448-3.338)	**0.000
Dermatological Symptoms				
Rash	40 (20%)	41 (24%)	0.832 (0.508-1.362)	0.464
Pruritus	75 (38%)	27 (16%)	3.375 (2.044-5.572)	**0.000
Redness at injection site	63 (32%)	85 (49%)	0.505 (0.331-0.771)	**0.001
Alopecia	18 (9%)	20 (11%)	0.939 (0.842-1.826)	0.852

Pearson's Chi-Square Test/Chi-Square Goodness-of-Fit * Significant p-value < 0.05; ** Highly Significant p-value < 0.005; ns = non-significant

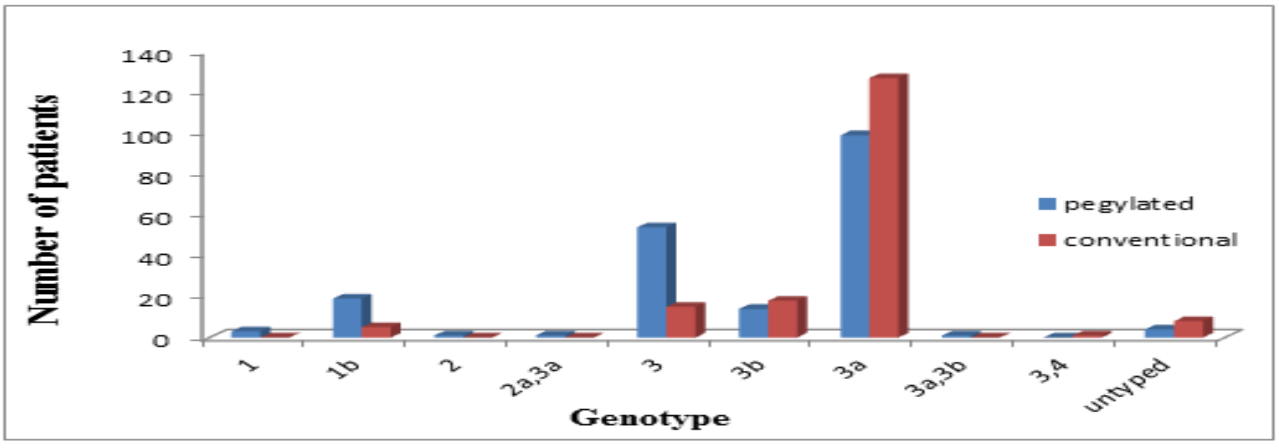

Fig. 1: Viral genotype of HCV affecting the patients in both arms of interferon therapy

Table 3: Comparison of sustained virological response with different parameters

Parameter		RNA Detected at 6 month after completion of therapy	
		Peg-interferon with Ribavirin N=196	Interferon with Ribavirin N=174
Age	<45y	20/136 (14.70%)	29/113 (25.66%)
	>45y	18/60 (30%)	29/61 (47.54%)
Gender	Male	13/97 (13.40%)	31/96 (32.30%)
	Female	25/99 (25.25%)	27/78 (34.62%)
Weight	<60kg	16/80 (20%)	22/65 (33.85%)
	>60kg	22/116 (18.97%)	36/109 (33.03%)
Education	Illiterate	18/110 (16.36%)	37/106 (34.91%)
	Literate	20/86 (23.26%)	21/68 (30.88%)
Marital status	Single	3/25 (12%)	8/28 (28.57%)
	Married	35/171 (20.5%)	50/146 (34.25%)
SVR achieved in patients with genotype	Total	158 (80.61%)	116 (66.67%)
	1,1b	1/22 (4.55%)	3/5 (60%)
	2,2a	1/5 (20%)	1/8 (12.5%)
	3,3a,3b	36/169 (21.30%)	54/161 (33.54%)
Viral Load	$< 2 \times 10^6$ copies/ml	30/173 (17.34%)	33/120 (27.5%)
	$>2 \times 10^6$ copies/ml	8/23 (34.78%)	25/54 (46.30%)
Cirrhosis	Yes	5/16 (31.25%)	4/9 (44.44%)
	No	33/180 (18.33%)	54/165 (32.73%)
Hepatic Damage	Yes	15/46 (32.61%)	12/25 (48%)
	No	23/150 (15.33%)	46/149 (30.87%)
Fibrosis	Yes	10/39 (25.64%)	12/25 (48%)
	No	28/157 (17.83%)	46/149 (30.87%)

Table 4: Treatment outcomes of Ribavirin with peg-interferon and conventional interferon regimen in HCV patients

Parameters		Peg-interferon with Ribavirin N=196	Interferon with Ribavirin N=174
Clinical Outcome	Improved	172 (87.75%)	130 (74.71%)
SVR		158 (80.61%)	116 (66.67%)
ALT response	Start of treatment	77.56±53.64	97.24±67.04
	End of treatment	35.33±21.02	33.04±21.97
	Percentage (%) reduction	54.45%	66.02%
AST response	Start of treatment	71.88±44.67	74.39±52.92
	End of treatment	37.69±23.29	33.02±29.11
	Percentage(%) reduction	47.57%	55.61%
Hb level	Start of treatment	13.34±1.85	16.40±30.17
	End of treatment	12.16±7.86	11.20±1.76
	Percentage(%) reduction	8.85%	31.71%

DISCUSSION

Cytokines that have antiviral and immune-modulating properties are essential part of chronic hepatitis C treatment. Two forms of interferon used in chronic HCV infection; i.e. conventional interferon, also called standard or unmodified interferon (IR), and pegylated-interferon (PIR). Pegylated-interferon have inert molecule polyethylene glycol attached to them that increases its half life, safety, tolerability, pharmacokinetics and efficacy. These benefits have been translated in clinical settings in the form of improvement in patient's disease pattern (Camma *et al*., 2004). According to present study, genotype 3 was found to be more prevalent in Gujranwala and adjacent areas particularly genotype 3a followed by genotype 3b. Another report corroborated this finding, focusing on HCV prevalence in Punjab province, Pakistan (Aziz *et al*., 2013, RUBI GHAZALA1*, 2015). Among the co-morbidities, hypertension was found to be most common complication along with HCV infection, followed by joint disorder and diabetes mellitus (DM), risk factors for further complication (Saleem *et al*.). The association between HCV and DM has been suggested before and is thought to be related to HCV induced immune reaction against β-cells that causes DM (Lecube *et al*., 2006). DM affects the response to antiviral agents with PIR/Ribavirin in HCV patients (Abdel Moneim A., 2015). People are prone to high risk of HCV infection

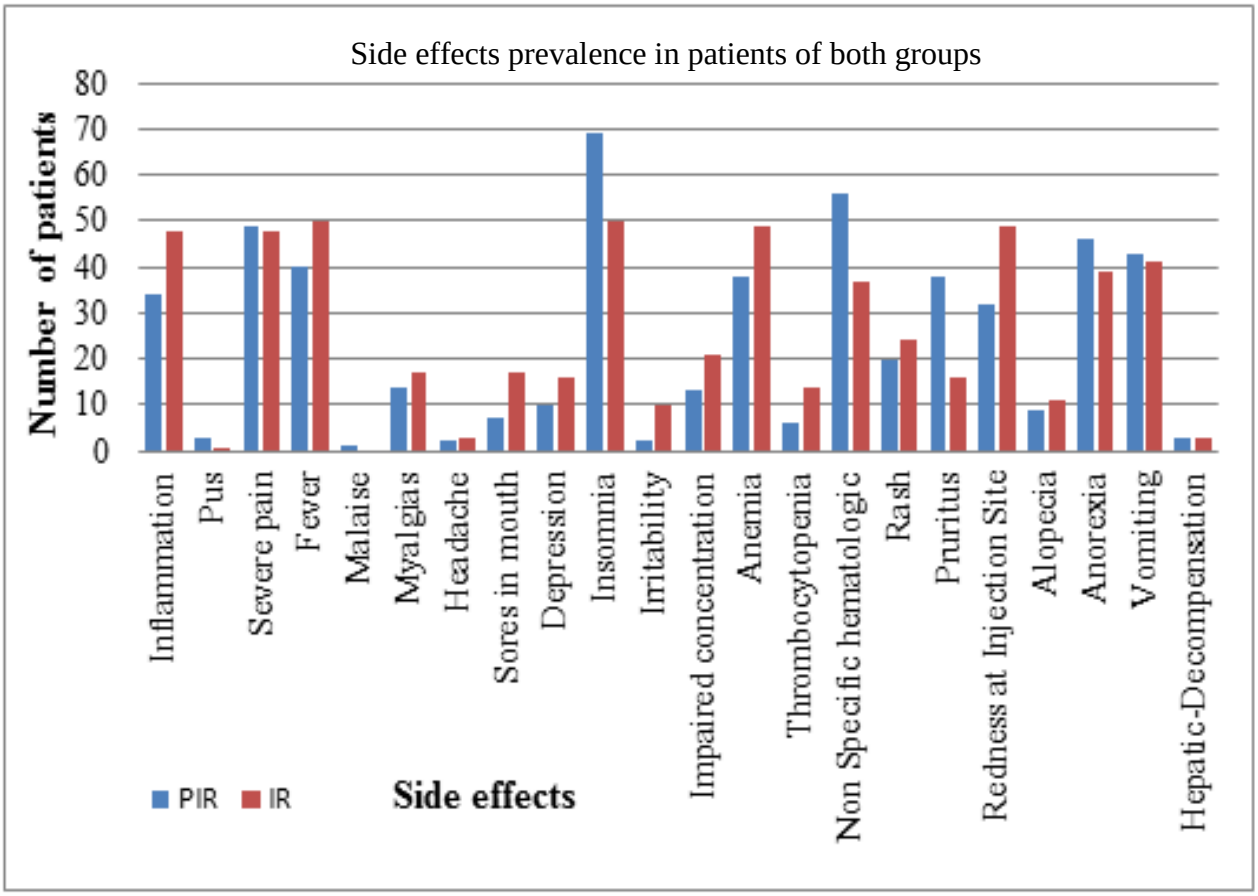

Fig.2: Side effects observed in Patients underwent treatment

undergoing repeated blood transfusion, dental and surgical procedure. In Gujranwala major risk factor involved in spread of HCV was unsafe dental procedure, with other factors like surgery and shaving outside from community barbers. In a country like Pakistan, where most of the people are illiterate and other ritual practices are common, adherence to therapy becomes difficult owing to low socio-economic factors. Along with these factors, frequent use of injections by quacks and dispensers for possible treatment and drug abuse is also contributing factor for disease progression as reported by Qureshi, S., *et al*. (Qureshi *et al*., 2009). Our study suggested that PIR therapy was superior to IR as this group achieved higher SVR rate and similar findings were observed by (Manns *et al*., 2001, Laguno *et al*., 2004). Likewise, results demonstrated that biochemical response was significantly improved at the end of therapy, irrespective of the achievement of SVR. Biochemical response improves with the duration of therapy as the duration of therapy increases >6 months (Saleem *et al*., 2017). Normalization of ALT and AST were shown to be better in PIR arm as compared to IR arm also supported in another study by Reddy, K.R., *et al*(Reddy *et al*., 2001). During the course of therapy irrespective of the regimen, ALT and AST values were found higher at the first month but normalized with the advanced therapy indicating improvement in liver histology. Poynard *et al*(Poynard *et al*., 1997)has demonstrated similar observation, that PIR with Ribavirin slowed down the progression of cirrhosis by improving hepatocyte function. During interferon treatment, elevation in hepatic enzymes is a normal phenomenon, but in cases of fatal hepatic failure LFTs should be checked every month. In case of hepato-toxicity, dosage adjustment is the primary approach to be considered. Male population of the city showed significant achievement of SVR as compared to female contrary to Poynard*et al*., opposite observation (Poynard *et al*., 2001). The plausible explanation may be the belief in the family, or psychological factor that may be involved. Moreover, side effects may be involved, which resulted in reduced adherence to therapy e.g. anemia found more commonly in female patients of both the arms in this study. Additionally, SVR achievement was not found optimal in overweight patients of >60kg, as compared to patients having normal weight or in the required range i.e. <60kg (Qureshi *et al*., 2009).

Side effect profiles showed that the PIR based regimen has fewer side effects than conventional or standard interferon based regimens. Patient must be instructed carefully about possible side effects and schedules of regimen. Regular follow up to monitor treatment progress

should also be planned, to minimize the risk of treatment discontinuation (Antonio, 2011). Patient's guidance program can alleviate this problem; they should be guided about premedication with Acetaminophen in case of fever, as well as adequate hydration. Fever that lasts for more than a day may indicate infection. Among the neuropsychiatric side effects, depression and insomnia were most commonly reported symptoms. The mechanism of interferon based depression is thought to be related with changes in serotonin activity in the brain. It is speculated that levels of tryptophan from which serotonin originates, decreases during interferon therapy. Selective serotonin reuptake inhibitors (SSRIs) may be beneficial for depression in chronic HCV patients. Insomnia is caused by the effect of interferon on hypothalamic pituitary adrenal axis and altering melanin level in brain. In this study, depression was more frequently associated with IR based regimen as compared to PIR. Among other neuropsychiatric problems i.e. impaired concentration and irritability is also associated with change in neurotransmitters within the brain by interferon (Fried, 2002). Hematological disorders are most frequent side effects of interferon-based regimens that sometimes can lead to treatment discontinuation the commonest one is anemia. In this study anemia was more commonly associated with IR based regimens. Ribavirin is transported in to RBCs and activates Ribavirin triphosphate that is not hydrolyzed by erythrocytes and causes oxidative damage to erythrocytes and extra vascular hemolysis (Dusheiko, 1997). This decrease in hemoglobin can cause fatigue and sense of general weakness. To alleviate this side effect recombinant erythropoietin is used to improve patient's Hb level (Antonio, 2011, De Franceschi *et al*., 2000). Thrombocytopenia was also more prevalent in IR treated patients than PIR group. Thrombopoietin receptor agonists can be helpful in raising platelet count in thrombocytic patients as FDA approved agent Eltrombopag is helpful (McHutchison *et al*., 2007).

CONCLUSIONS

The present study has shown more safety, efficacy and better tolerability of peg-interferon/Ribavirin based regimen as compared to conventional interferon/Ribavirin in management of chronic Hepatitis C (HCV) patient reporting with genotype 3a. The study necessitates the launching of awareness campaigns and patient assistance programs to lessen the discontinuation of therapy and to try novel combination with better safety and efficacy with minimum side effects.

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