

## ORIGINAL ARTICLE

## COMPARATIVE THERAPEUTIC RESPONSE TO PEGYLATED INTERFERON PLUS RIBAVIRIN VERSUS INTERFERON ALPHA-2b IN CHRONIC HEPATITIS C PATIENTS

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**Background:** Hepatitis C is an epidemic worldwide since discovery in 1989. Conventional interferon alpha-2b plus Ribavirin therapy was started in 1998 but over all sustained viral response (SVR) rates are much below the desired rates to eradicate the diseases and stopping its epidemic. This study was conducted to access the therapeutic and cost-effectiveness of long acting pegylated interferon alpha-2b plus Ribavirin therapy verses conventional interferon alpha-2b plus Ribavirin. **Methods:** This comparative study was done at PAF Hospital Shorkot Cantt from July 2005 to July 2008. One hundred anti-HCV positive patients were selected randomly for the study according to willingness due to cost affordability of the patients for conventional interferon. Group-A was labelled as pegylated interferon alpha-2b plus Ribavirin group, and Group-B interferon alpha-2b plus Ribavirin group. Both groups were given treatment for 24 weeks. Early virological response (EVR) was accessed at 12 weeks of treatment. Sustained virological response (SVR) in both the groups was done at 24<sup>th</sup> week during the treatment and 6 monthly after treatment for 2 years. Initially non-responders and relapsed patients within 2 years of treatment were re-treated for 24 weeks with the same treatment. In both groups non-responders and relapsed patients were labelled as resistant patients. Both groups were followed with same protocol for 2 years. **Results:** Out of 100 patients included in the study, 34% were females and 66% were males. Group-A patients over all showed 94% SVR as compare to 80% in Group-B in 2 year follow-up. Group-A showed 6% resistant patients as compare to Group-B (20%). Conventional interferons were better tolerated. Higher incidence of side-effects was seen in Group-A. **Conclusion:** Pegylated interferon plus Ribavirin showed 94% SVR in 2 years. Pegylated interferon plus Ribavirin is the treatment of choice.

**Keywords:** Anti-HCV, ELISA, PCR, SVR, Pegylated-interferon, Interferon Alpha-2b, Ribavirin

### INTRODUCTION

Hepatitis C is considered pandemic worldwide with a global prevalence of around 2% to 3%, i.e., around 123–170 million people worldwide carry HCV infection. There is high degree of geographical variation in its distribution.<sup>1</sup> The prevalence of HCV infection is low, in the United Kingdom, Scandinavia (0.01% to 0.1%), Americas, Western Europe, Australia, and South Africa (0.2% to 0.5%). Intermediate prevalence is seen in Eastern Europe, Mediterranean, Middle East, and India. Other countries with intermediate prevalence include Brazil, Eastern Europe, parts of Africa, and Asia.<sup>2</sup> Egypt has a high prevalence of HCV infection (17% to 26%) besides Hubei, Mongolia, and Pakistan.<sup>3,4</sup>

In Pakistan approximately 10 million people (6% of the population) have been living with HCV infection. The HCV epidemic in Pakistan is continuously progressing due to lack of education, awareness of diseases, shortage of medically qualified and scientifically trained health care workers, lack of basic health infrastructure along with very low socioeconomic conditions.<sup>5</sup>

Hepatitis C was isolated from non-A non-B hepatitis viruses in 1989 by Choo and co-workers of Chiron cooperation Group.<sup>6</sup> Auch RD *et al* developed

ELISA in 1991 for detection of anti-HCV anti bodies in blood.<sup>7</sup> Bukh J *et al* in 1992 invented PCR for detection of HCV RNA in human blood.<sup>8</sup>

HCV is a single strand RNA virus of about 3,000 amino acids polypeptides. It belongs to Flaviviridae family and is only hepac virus genus in Flaviviridae family.<sup>9</sup> Change in sequence of amino acids in RNA strands results in generation of multiple genotypes labelled as 1, 2 etc. and numerous sub-genotypes labelled as 1a, b, c etc. Until now 6 major genotypes (1–6) and numerous sub-genotypes have been isolated. The most predominant HCV genotype in Pakistan is type 3 (75 to 90%) followed by 1, 2 and 5.<sup>10</sup>

In Pakistan major routes of HCV transmission are blood transfusion, daily face and arm pits shaving at community barber shops, parenteral drug abuse, dental and surgical procedures, tattooing, haemodialysis units, improper disposal of used needles and same needles are re used in multiple people and sexual transmission.<sup>11,12</sup> After exposure, up to 80% of the people develop chronic infection. The progression of disease is variable, occurring over a 20–50 years period. Although some people may never progress, about 30% will develop liver cirrhosis in 20–30 years.<sup>13</sup>

Eradication of the virus requires prolonged treatment with antiviral agents to eliminate the virus in the serum (phase 1 decay) and hepatocytes (phase 2 decay). Response to therapy is measured by a sustained virologic response (SVR), which is defined as the undetectable viral levels 6 months after completion of therapy.<sup>14,15</sup>

Therapeutic options have evolved from the initial 3-times weekly interferon monotherapy to the current optimal therapy consisting of pegylated (polyethylene glycol molecule) interferon (Peg) alfa in combination with ribavirin (RBV). Pegylated interferons have different pharmacokinetic properties than non-pegylated interferon, including much longer half-life.<sup>16</sup> Pegylated interferon alpha-2b has more than thirteen times long half life which is great advantage over interferon alpha-2b to maintain the uniform levels throughout the week with once weekly injection pharmacodynamic and pharmacokinetic comparison of interferon alpha-2b and pegylated interferon alpha-2b are given in Table-1.<sup>17</sup>

**Table-1: Kinetic comparison of interferon alpha-2b and pegylated interferon alpha-2b**

	Interferon alpha-2b	Pegylated interferon alpha-2b
Time to peak serum levels (Hr)	7.3-12	80
Absorption half life (hours)	2-3	50
Volume of distribution (L)	31-73	8-12
Clearance (L/hr)	6.6-9.8	0.05-0.10
Elimination Half Life (Hr)	3-5	65

## MATERIAL AND METHODS

This study was conducted in PAF Hospital Shorkot Cantt from July 2005 to July 2008. A total of 700 anti-HCV positive patients reported during this period. Patients' anti-HCV status was confirmed by RCR. All patients were subjected to investigations like blood complete picture, ultrasound abdomen, LFTs, serum electrolytes, coagulation profile, urine routine examination, serum lipid profile, serum protein profile and blood sugars. One hundred patients, within the age group of 17-50 years, with normal or mildly deranged liver functions, with no features of overt chronic liver disease and without any co-morbid conditions of diabetes, hypertension and ischemic heart disease were selected for this study. Patients were given the treatment option of both pegylated interferons and conventional interferons therapy in combination of Ribavirin. A group of 50 alternate patients opting for pegylated interferons plus Ribavirin therapy were grouped in one group, and the 50 alternate patients opting for conventional interferons plus Ribavirin regimen, purely due to their poor socioeconomic status were included in other group. Ethical approval from hospital administration was obtained and written informed consent was taken from all the patients.

Group A was given Pegylated interferon alpha-2b 150 µg subcutaneously once weekly with Ribavirin 800 to 1,200 mg daily. Group B was given Interferon alpha-2b, 3 million units subcutaneously thrice weekly with Ribavirin 800 to 1,200 mg daily.

All patients irrespective of their gender were given therapy for six months. Physical examination, blood complete picture with platelet count, and coagulation profile were LFTs were performed fortnightly in both groups. Response to treatment of both groups was accessed on the basis of:

**Early virological response (EVR):** A 2 log or greater reduction in Hepatitis C RNA levels 12 weeks after the initiation of antiviral therapy;

**Sustained virological response (SVR):** Absence of detectable Hepatitis C RNA at least 24 weeks after completion of therapy;

**Non-responders:** Lack of any response to the treatment at the end of 24 weeks of treatment;

**Relapse:** Patients who again became PCR for HCV RNA positive within 2 years after gaining SVR.

Qualitative PCR was done at 12 weeks, 24 weeks and 2 years of therapy to access the response of therapy. The adverse effects of treatment among both the groups were also documented. Patients of both the groups who remained PCR for HCV RNA negative after two years were declared as disease free. The relapse patients from both groups during treatment or within 2 years of treatment and the non-responders were subjected to re-treatment for 24 weeks.

## RESULTS

Out of the 100 patients included in the study, 34% were females and 66% were males. Sixty-one percent of the patients were in the age group of 35-45 years. In group A (pegylated interferon) 40 (80%) showed EVR in 12 weeks and 45 (90%) became PCR negative after 24 weeks of treatment. Five (10%) remained non-responder and 5 (10%) became PCR positive for HCV RNA within 2 years. When non-responders of group-A 5 (10%) were given treatment up to 48 weeks and (10%) relapsed patients with 2 years were retreated for 24 weeks (total 48 weeks) out of 10 (20%) of these patients of group-A 47 (94%) finally became PCR for HCV RNA negative and remained negative for 2 years; they were declared SVR or cured patients. Only 3 (6%) patients of group-A were remained PCR for HCV RNA positive after 48 weeks of treatment. They were labelled as resistant to pegylated interferon plus Ribavirin therapy.

In group B (conventional interferon plus Ribavirin) patients 32 (64%) became PCR for HCV RNA negative within 12 weeks and 36 (72%) became PCR for HCV RNA negative within 24 weeks. Fourteen (28%) were non-responders, and 6 (12%) initially responders to treatment developed relapse within 2 years. Then 14 (28%) initially non-responders were given

extended treatment for 48 weeks and 6 relapse patients were retreated for 48 weeks. In 48 weeks out of 20 patients 10 more patients (50%) of group B PCR for HCV RNA, remained negative PCR for HCV RNA for 2 years. Hence 40 (80%) patients of group B were declared cured after treatment and on 2 years follow up. Ten (20%) were labelled as resistant group B regimen.

There is a clear difference of response to pegylated interferon plus Ribavirin (Group-A) (SVR) cured rates 47 (94%) as compare to interferon alpha-2b plus Ribavirin 40 (80%). Only 3 (6%) patients showed resistance to group A regimen as compare to group, i.e., 10 (20%) regimen. As highlighted in Figure-1.

Both the groups of patients had almost similar adverse effects during treatment as group A body aches 30 (60%) malaise 35 (70%) fever 20 (40%) bone marrow suppression anaemia 25 (50%) granulocytopenia 15 (30%) Thrombocytopenia 10 (20%) depression 14 (28%)

Group-B Body aches 20 (40%) malaise 25 (50%) fever 25 (50%) depression 10 (20%) bone marrow depressions anaemia 15 (30%) thrombocytopenia 7 (14%) granulocytopenia 13 (26%) anaphylaxis 1 (2%).

Only two patients 02(4%) of group A required blood transfusion and 1 (2%). 2 (4%) of each groups were given erythropoietin and Granulocyte colony stimulating factor for bone marrow suppression. None of the patients of group A and B developed chronic liver disease within 2 years of follow up.

Significant more adverse affects in group A are likely due to sustained levels of interferon throughout the week due to its long half life or may be secondary to ethylene glycol edition. As shown in Table-2. All 13 resistant patients of both the groups were subjected to genotyping. All of them were found to be genotype 1.

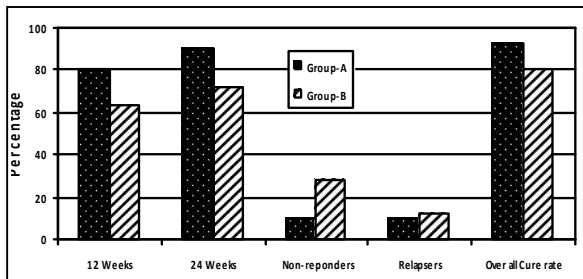


Figure-1: Response to treatment

Table-2: Adverse effects observed

Effects	Group-A		Group-B	
	No.	%	No.	%
Body-aches	30	60.0	20	40.0
Malaise	35	70.0	25	50.0
Fever	20	40.0	25	50.0
Anaemia	25	50.0	15	30.0
Granulocytopenia	15	30.0	13	26.0
Thrombocytopenia	10	20.0	7	14.0
Blood Transfusion	2	4.0	1	2.0
Erythropoietin and GCSF	2	4.0	1	2.0
Depression	14	28.0	10.0	20

## DISSCUSION

The current study was conducted to see the comparative therapeutic response to pegylated interferon plus Ribavirin (group-A) versus interferon alpha-2b plus Ribavirin (group-B) in chronic Hepatitis C. This study has shown that group-A has better SVR rates with initial 24 weeks treatment and in extended treatment to initially non responder patients and patients had relapse within 2 years of treatment. Group-A SVR in 24 weeks was 45 (90%) versus Group-B it was 36 (72%). Initially non-responders in group-A were 5 (10%) but the non-responder in group-B were 14 (28%). Relapse rates within 2 years in group-A was 5 out of 50 (10%) and in group-B was 6 (12%)

After extended treatment to non responders and re treatment of relapsed patients, group-A patients for 24 weeks revealed over all SVR 47 (94%) and it was 40 (80%) in group-B. Only 3 (6%) were resistant to treatment in group-A as compare to group-B 10 (20%) patients. Over all therapeutic SVR to peg interferon alpha-2a plus Ribavirin were 56% to 63% in Fried MW *et al* and Hadziyanms SJ *et al*.<sup>18,19</sup> But as compared to with interferon alpha-2b plus Ribavirin therapy SVR (45%). Simin M *et al* study revealed over all SVR 63% with pegylated interferon alpha-2a plus Ribavirin as compared to conventional interferon plus Ribavirin SVR 43% in 48 weeks, there was only 13% increase in SVR after re-treatment of non-responders of conventional therapy group.<sup>20</sup> Manns MP *et al* study in 2001 revealed SVR 41% with interferon alpha-2b plus Ribavirin as compare to peg interferon plus Ribavirin 42% in genotype 1 and 80% in genotype 2 and 3 in 24 weeks.<sup>21</sup> None of these comparative studies mentioned above followed their patient's up-to 2 years to declare them disease free or cured.

Current study has shown much better results in both the groups as compared with above mentioned studies. Group-A revealed (94%) SVR/cured after 2 years while group-B SVR/cured rate after two years was 80%. Only 3 (6%) patients were resistant in group-A while 10 (20%) were resistant in group-B which is much less than comparative studies included in the text and the success rates of both the groups of current study are much better. Resistant rates of both the groups are much less than world wide studies.

The better results in both the groups of current study are likely due to predominant genotype C 3 (about 75%) in Pakistan<sup>10</sup> which is less resistant to conventional interferon and pegylated interferon. Selection of patients in early stage of Hepatitis C infection, less number of patients in both the groups, racial genetic makeup might have played role in the better response in current study. Alcoholism, obesity and dietary habits decrease the response to interferon which is much lesser problem of

our society and might have been contributed for better response in the current study.

All 13 resistant patients of both the groups were subjected to genotyping. All of them were found to be genotype 1, which is the most resistant genotype of Hepatitis C virus to any type of interferon and Ribavirin therapy all over the world.

The significant more adverse effects of the treatment in group-A patients are likely due to long half life of pegylated interferon alpha-2b or due to addition of ethylene glycol. But in spite of these high adverse effect as compare to group-B. Much better SVR with pegylated interferon alpha-2b plus ribavirin therapy makes it the treatment of choice for the treatment of the chronic hepatitis C patients.

## CONCLUSION

Sustained viral response/cure rates are much better in pegylated interferon plus Ribavirin (group-A). This regimen will help in decreasing the number of HCV infected patients and further spread of Hepatitis C in the community, and will also decrease the morbidity and mortality from the disease itself by decreasing the chronic liver disease, cirrhosis of liver, HCC and preventing the involvement of other body organs.

Epidemic of HCV cannot be prevented from the world until and unless scientists succeed in preparing the vaccination for prevention of the disease. Till then, major routes of spread must be addressed strictly.

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