

Efficacy of Biosimilar Pegylated Interferon Alpha 40 KD (Peg INF) in Chronic Hepatitis C Infection

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Abstract—Introduction: Pegylated Interferon and Ribavirin combination is standard of care in the management of chronic HCV infected patients. Efficacy of the therapy is judged by the ability to achieve biochemical and virological response as judged by RVR, EVR, ETR and SVR. Objective: To evaluate the efficacy of newly marketed biosimilar Pegylated Interferon Alpha 40KD (Peg INF) in chronic HCV patients. Materials and methods: This was observational, prospective multicentre study to evaluate the ability of biosimilar pegylated interferon alfa 2a (40KD) along with Ribavirin (weight based) to achieve SVR. The enrolled patients were separated into Naïve (A), Relapsers (B) and Non Responders (C) based on the previous history of interferon exposure and its response. The RGT was followed on ALT and RVR, EVR, ETR and SVR. Results: As per protocol analysis estimated SVR for three groups is 86.6% for naïve, 89.4% for relapsers and 52.4% for non-responders to standard interferon. Conclusion: It is concluded that Bio-similar pegylated interferon alfa-2a (40kD) along with Ribavirin has good anti-viral efficacy in Naïve, Relapsers and Non-responders to standard IFN of chronic HCV infected patients requiring treatment.

Keywords—SVR (Sustained virological response), NR (Nonresponders), Pegylated Interferon.

I. INTRODUCTION

HEPATITIS C (HCV) affects 10 million Pakistani population [1]. It is responsible for 25-30% cases of cirrhosis globally that is associated with increasing risk of hepatic decompensation and hepatocellular carcinoma (HCC) [2]. Sustained virological response (SVR) after antiviral therapy may halt the progression of fibrosis with lower risk of developing HCC and improves survival [3]. However, the SVR rates depend upon many host and virus related factors including age, gender, obesity, HCV genotype, baseline viral load, and stage of liver fibrosis [2]-[4] and also response to previous HCV treatment. Treatment with pegylated interferon (Peg-IFN) and ribavirin (RBV) is considered as the standard of care for hepatitis C virus management, also it is associated with 40-50% and up to 80% SVR in HCV genotype 1 and 2/3 (naïve patients) respectively [5]-[7]. Once antiviral therapy for chronic hepatitis C virus (HCV) infection has been started, the likelihood that a patient will achieve a sustained virologic

response (SVR) can be predicted by the virologic responses during therapy. The rapidity of the virologic response also appears to be an important predictor of an SVR.

Two pegylated interferon brands are currently available, first is PEG IFN α 2a, a 40 KDa in which branched polyethylene glycol (PEG) moiety attached to IFN α 2a by a stable amide bond, that consist of six positional isomers and second is PEGIFN α 2b, 20 KDa [9]. Both are recommended to prescribe with ribavirin for HCV Management. The aim of this study is to assess the biosimilarity of pegylated interferon, Peg-IFN which is pegylated IFN α 2a, 40KDa by BF Biosciences, Pakistan used in the management of chronic HCV patients. Here, we judge the efficacy of Peg-IFN in treatment-naïve, non-responders, and relapsers to standard IFN patients with CHC by the ability to achieve biochemical and virological response as judged by RVR, EVR, ETR and SVR.

II. TERMS AND ABBREVIATIONS' DEFINITIONS [10]

Sustained Virological Response (SVR) is undetectable HCV RNA level (<50 IU/ml), 24 weeks after treatment.

Rapid Virological Response (RVR) is undetectable HCV RNA in a sensitive assay (lower limit of detection 50 IU/ml) at week 4 of therapy, maintained up to the end of treatment.

Early Virological Response (EVR) is HCV RNA detectable at week 4 but undetectable at week 12, maintained up to end of treatment.

Delayed Virological Response (DVR) is more than 2 log₁₀ drop but detectable HCV RNA at week 12, HCV RNA undetectable at week 24, maintained up to end of treatment.

Null Response (NR) is less than 2 log₁₀ IU/ml decrease in HCV RNA level from baseline at 12 weeks of therapy.

Partial Response (PR) is more than 2 log₁₀ IU/ml decrease in HCV RNA level from baseline at 12 weeks of therapy but detectable HCV RNA at weeks 12 and 24.

Breakthrough (BT) is reappearance of HCV RNA at any time during treatment after virological response.

III. MATERIALS AND METHODS

A. Subjects

A multicenter observational study was planned to evaluate the ability to achieve SVR with the biosimilar pegylated interferon alfa-2a (40 KD). Enrolled patients have been divided into 3 groups A, B, C for Naïve, Non responders, and Relapsers to standard interferons respectively. Patients from Post Graduate Medical institute, Lahore General Hospital,

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Lahore, and the various collaborating centers from August 2009- December 2012 had enrolled in the study.

Eligible patients were ≥ 18 years of age with Chronic Hepatitis C (CHC) infection who were naïve, non-responders or relapsers to prior therapy with conventional interferon alfa 2a or alfa 2b and ribavirin. The diagnosis of CHC was based on detectable anti-HCV antibody (by ELISA-IV or MEIA method) and serum HCV RNA by PCR (COBAS Amplicor, HCV qualitative assay). Patients with significant liver disease, including portal fibrosis (F2), bridging fibrosis (F3) and cirrhosis (F4) were eligible for the study in the absence of prior episode of hepatic decompensation given that they have normal liver function evident by serum bilirubin <2 mg/dl, serum albumin ≥ 3.5 mg/dl and platelet count $\geq 75,000/\text{mm}^3$. Patients excluded from study who had concomitant HBV, HDV or HIV infection, HCV related decompensated cirrhosis; defined as ascites, portosystemic encephalopathy, hepatorenal syndrome, HCC and recurrent variceal bleed, Major psychiatric illness Hemoglobin $< 12\text{gm/dl}$ in males and $< 11\text{gm/dl}$ in females, WBC counts $< 2.5 \times 10^3/\text{L}$ or neutrophil count < 1500 cells/ml, Platelets count $< 75,000/\text{dl}$, Serum creatinine > 1.5 mg/dl, Concomitant metabolic or autoimmune liver disease, post liver transplant patient, pregnant and lactating mothers, uncontrolled seizures, active drug user, severe heart disease or other absolute contraindications for the treatment. Patients with inadequate contraception or those not consenting to the study were also excluded. We did not offer treatment to patients above 65 years of age unless requested by the patient.

B. Treatment

Patients were treated with subcutaneous injection of Pegylated interferon alpha 2a (Peg-INF) 180 mcg/week and oral weight based (15mg/kg) Ribavirin in two to three divided doses daily, response guided therapy was started, patients with genotype 3 were followed up with qualitative PCR at week 4, 12 and 24/48 during the treatment and 24 weeks after the end of therapy. For genotype 3 treatment naïve patients, who achieved RVR were treated for 24 weeks, patients who failed to achieve RVR and achieve EVR they were treated for 48 weeks. Those who failed to achieve EVR were declared non responders and treatment was stopped, for relapsers and non-responders to standard interferon duration of treatment was one year irrespective of the fact whether they achieved RVR or EVR. A real-time PCR-based assay, with a lower limit of detection of 50 IU/ml was used.

C. Efficacy Assessments and End Points

Four landmarks have been decided

1. RVR
2. EVR [Those who do not achieve RVR]
3. ETR
4. SVR

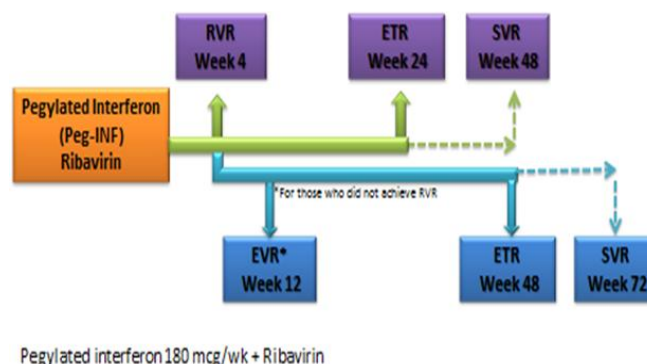


Fig. 1 Study design showing efficacy assessment landmarks and endpoints

D. Safety Assessments

At each visit, the patients were assessed for clinical, hematological and bio-chemical side effects of pegylated interferon alpha-2 and ribavirin. These parameters were assessed at weeks 2 and 4 of therapy and at 4 to 8 week intervals thereafter. Thyroid stimulating hormone (TSH) and free thyroxine levels were measured every 12 weeks while on therapy.

Pregnancy tests were performed every 12 weeks for female subjects and spouses of male subjects. The protocol permitted dose modification (a 25%, 50%, or 75% reduction in the assigned dose) for patients who had clinically significant adverse events or important abnormalities in laboratory values. If hemoglobin fell below 10g/dl, subcutaneous injections of erythropoietin at doses of 4000 IU - 12000IU/week were given for managing anemia with reductions in dose of RBV in accordance with product labeling if there was no response to erythropoietin. Granulocyte colony stimulating factor (G-CSF) was used to correct white blood cell count when absolute neutrophil count (ANC) was less than 750 cell/mm³. Patients were withdrawn from the study if they missed four consecutive weeks of treatment or if there was concern about safety. Data was analyzed by SPSS version 19.

E. Ethics

The Institutional Review Board and Ethics Committee of the of Post Graduate Medical institute, Lahore General Hospital, Lahore, approved the research protocol. Subjects were enrolled only if they signed the informed consent form. Use of PEGINF in human subjects was authorized by the Ministry of Health, Pakistan.

F. Statistical Methods

Efficacy and safety analyses included per protocol analysis. All analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).

IV. RESULTS

A total of 209 patients were enrolled in the study, of which 126 were men and 83 were women. Patients' major baseline

demographic and disease characteristics are presented in Tables I and II.

TABLE I
DEMOGRAPHICS OF PATIENTS

	Naïve(n=127)	Relapsers(n=61)	Non-Responders(n=21)
Age, Years	40.55 (SE± 0.97)	41.68 (SE ± 1.6)	40.90 (SE ±2.6)
BMI	25.72 (SE ± 0.39)	26.08 (SE ± 0.97)	26.80 (SE ± 1.59)
Male (126)	70	42	14
Female (83)	57	19	07

TABLE II
GENOTYPES OF STUDIED PATIENTS

Genotype	Patients (%age)
3	119 (86.3%)
2	12 (08.6%)
1 - 4	8 (03.3%)

TABLE III
RESPONSE OF THERAPY

	RVR	EVR	ETR Week24	ETR week48	SVR Week 48	SVR Week 72	Total SVR	Relapsers	NR	Lost to follow up
Naïve (n 127)	77.9% (99/127)	57.7 % (15/26)	82% (81/99)	54.2% 13/24	80.8% (80/99)	45.8% (11/24)	86.6% (91/105)	3.2% (3/94)	8.6% (11/127)	17.3% (22/127)
Relapsers to standard INF (n61)	80% (49/61)	70 % (7/10)	-----	78.6% (44/56)	-----	89.4% (42/47)		4.3% (2/47)	5.1 % (3/59)	20% (12/61)
Non responders to standard INF (n21)	47.6% (10/21)	33.3% (3/9)	-----	68% (13/19)	-----	52.6% (10/19)		3/19 (15.8)	31.6 % (6/19)	9.5% (2/21)

V. DISCUSSION

In the current study, we have used a locally manufactured pegylated IFN, Peg-INF (IFN α 2a, 40KDa by BF Biosciences, a subsidiary of Ferozsons laboratories limited, Raiwind, Lahore, Pakistan) in combination with standard doses of RBV (Xolox) in treatment of patients with CHC. The effectiveness of this regimen has been previously shown in literature. This study confirms previous results, determining that use of this newly developed pegylated IFN is effective and safe for treatment naïve cases of CHC, with better results among relapsers and non-responders to standard IFN showing its parallel efficacy in all three treatment groups.

Furthermore, in addition to the bothersome and often severe adverse effects, patients have to deal with the expenses of treatment. Some patients may necessitate frequent injections of erythropoietin or G-CSF which further augments to treatment costs [11]. Also high rate of SVR in this study confirms previous reports from the Asian race [12]-[15]. However, part of this high SVR might be related to a thorough preliminary work up and screening, educational programs for treatment adherence to medications and a qualified clinical setting for management. Also, use of erythropoietin-stimulating agents and G-CSF decreased the rate of drop out and non-adherence, thus increasing patient satisfaction during treatment course.

In conclusion, it seems that the introduction of this new brand of locally produced PEG-IFN (Peg-INF) will be a better addition in HCV management with proven acceptable efficacy as our results support that this Biosimilar has comparable efficacy to original research molecule.

A. Among Naïve Patients (N 127)

A total of 91/105 (86.6%) achieved SVR, (3/94) 3.2% relapsed after treatment, (11/127) 8.6% were non-responders and (22/127) 17.3% lost to follow up.

B. Among Relapsers to Standard INF (N 61)

A total of (42/47) 89.4% achieved SVR, (2/47) 4.3% relapsed after treatment, (3/59) 5.1 % were non-responders and (12/61) 20% lost to follow up.

C. Among Non-Responders to Standard IFN (N 21)

A total of (10/19) 52.6% achieved SVR. 3/19 (15.8) relapsed after treatment, (6/19) 31.6 % were non-responders and (2/21) 9.5% lost to follow up.

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There are no other dualities of interest relevant to this manuscript.

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