ORIGINAL ARTICLE

Efficacy of Pegylated Interferon-alpha-2a in Chronic Hepatitis Delta: Experience from a Tertiary Care Hospital in Karachi

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Received on: 23 March 2024; *Accepted on*: 22 April 2024; *Published on*: 12 June 2024

Abstract

Background: Chronic hepatitis D (CHD) along with chronic hepatitis B (CHB) is an important cause of morbidity and mortality in patients with cirrhosis. It is a potentially curable infection that has long awaited a good treatment option.

Objective: To ascertain the efficacy of pegylated interferon (PEG-IFN)-alpha-2a in patients suffering from CHD. A tertiary care hospital experience from Pakistan.

Materials and methods: The study included 207 CHD polymerase chain reaction (PCR)-positive patients treated with PEG-IFN-alpha-2a between July 2020 and October 2022. Virological response rate (PCR negative) at weeks 24 and 48 was the primary endpoint. Secondary outcomes included partial response (>2 log reduction in PCR) and treatment failure rate (<2 log reduction in PCR).

Results: A total of 187 patients started PEG-IFN therapy, and 148 patients completed the assigned 48 weeks of therapy. Patients' mean age was 25.7 years with 65% being males. The virological response rate was 40.5% at week 24 and 32.4% at week 48. The partial response rate was 24% at both weeks 24 and 48. The treatment failure rate was 36% at week 24 and 44% at week 48. Hemoglobin, white blood cell (WBC) count, and total bilirubin were found to be predictive of treatment response. Side effects led to treatment discontinuation among eighteen patients and one patient died due to hepatic failure.

Conclusion: Therapy with PEG-IFN-alpha-2a shows suboptimal outcomes in patients with CHD. There is a strong need for more effective alternate therapies for CHD patients.

Keywords: Hepatitis delta virus, Outcomes, Pakistan, Treatment, Virological response.

Euroasian Journal of Hepato-Gastroenterology (2024): 10.5005/jp-journals-10018-1431

Introduction

The hepatitis delta virus (HDV) is unique in being a defective single-stranded RNA virus, which is dependent upon hepatitis B surface antigen (HBsAg) to use its envelope and thus enters the body of patients already infected with the hepatitis B virus (HBV). Nearly half a century since its recognition, there has not been much success in its treatment.[1] The lack of success in this area of high importance is multifold and may be attributed to various factors such as low prevalence in comparison to its counterparts, namely, the HBV and hepatitis C virus (HCV), along with a much more difficult population. Additionally, the adverse side effects may contribute to treatment adherence.[2] There are an estimated 10–20 million patients of coinfection of hepatitis D among an already huge number of 240 million individuals suffering from CHB. The seropositivity for HDV antibodies in Pakistani HBsAg-positive individuals is approximately 16.6%.[3,4] Among the HBV/HDV co-infected patients there is an accelerated rate of cirrhosis. Hepatitis delta virus causes more rapid rates of disease progression and early cirrhosis with a high incidence of hepatocellular carcinoma (HCC, 70–90%).[5]

Since its inception, pegylated interferon (PEG-IFN) is potentially the only viable therapeutic option for patients infected with chronic hepatitis D (CHD). It stems from the conventional interferon (IFN) therapy which was discontinued due to very limited efficacy.[6] In comparison to Standard IFN therapy, the pegylated form was found to be superior, efficacious, and associated with better sustained virological response (SVR) in these patients and might improve the outcome of patients with HDV.[7] Bulevirtide (hepatocyte entry inhibitor) and lonafarnib (farnesyl transferase inhibitor) are on the horizon as new HDV treatment options.[8] While INF-lambda is showing promising results both as mono and as a combination therapy.[9]

The response to PEG-IFN therapy is variable. Various studies have assessed varying dosages and durations of treatment for anti-hepatitis D virus (anti-HDV) therapy, utilizing both standard and PEG-IFN. However, most of these studies exhibit shortcomings in their selection processes, inadequate sample sizes, restricted data availability, or design-related deficiencies. Most of these studies have selection flaws, incomplete data, or design flaws. These studies evaluated various aspects of HDV therapy in terms

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How to cite this article: Butt N, Usmani MT, Hussain R, *et al*. Efficacy of Pegylated Interferon-alpha-2a in Chronic Hepatitis Delta: Experience from a Tertiary Care Hospital in Karachi. Euroasian J Hepato-Gastroenterol 2024;14(1):51–55.

Source of support: Nil

Conflict of interest: None

of variation in dose and treatment duration however most of them had shortcomings in one aspect or the other.[10–15] The response rate to HDV with standard or PEG-IFN has been on a scale of 18–41%. Nevertheless, the local studies exhibit a significant degree of antiquity and deficiency in statistical relevance.[7] Several studies have shown a fixed treatment duration of 12 months for the treatment of CHD.[10–15] Prolonging treatment duration more than this is not associated with a favorable outcome yet at the cost of unwanted and at times significant side effects. As some patients with HBV/HDV coinfection had cirrhosis since the start of treatment, prolonging the duration can lead to decompensation of their disease.

The present investigation endeavors to assess the therapeutic efficacy and adverse effects of PEG-IFN-alfa-2a administered to CHD patients for a 12-month treatment. This research aims to provide seminal insights that may serve as a foundation for future studies on a larger scale.

Materials and Methods

Patients who received treatment for CHD with PEG-IFN therapy for CHD at the Department of Gastroenterology and Hepatology, Jinnah Postgraduate Medical Center, Pakistan, from July 2020 to October 2022 were prospectively enrolled. An ethical review was sought before the conduction of the study. All participants gave informed consent.

Patients' Enrollment

The inclusion criteria were age ≥16 and ≤60 years, serological diagnosis of infection with HBV and HDV, HDV-RNA positive, no use of antiviral therapy in the past 6 months, compensated chronic liver disease (Child-Pugh score below 7 points or MELD below 12, no evidence of HCC). Patients who were treatment-experienced (received IFN-alpha-2a in the past 6 months), pregnant women, patients who have received immunosuppressant therapy, patients with underlying autoimmune disease, alcoholic liver disease, chronic kidney disease, congestive heart failure EF<45%, psychiatric disorders, significant cytopenia and any other factors that may impair the treatment adherence of such patients were excluded. Pretreatment serological tests were performed using the enzyme-linked immunosorbent assay (ELISA) technique on all patients for HBsAg, hepatitis B e-antigen (anti-HBe) antibody, quantitative HDV polymerase chain reaction (PCR), HBV viral load, and total anti-HDV antibodies (anti-HDV) were made using standard protocol. A standard dose (180 µg) of PEG-IFN-alpha-2a was subcutaneously (SC) administered in all treatment receivers during the study period once a week.

Monitoring

Patients were monitored every two weeks during the first 2 months. During these two months of follow-up, complete blood count along with liver function tests were performed fortnightly for possible treatment-related adverse events such as cytopenia, drug allergy, fever, etc. In the later phase, patients were followed up at 12-week intervals for biochemical response, virological response, treatment adherence, and other aforementioned treatment-related side effects.

Definition of Treatment Outcome

- End of treatment response (ETR)—serum HDV RNA below the detection limit at the completion of treatment (week 48).
- Partial virologic response—2 log IU/mL or more decrease in HDV-RNA levels from the pretreatment baseline within 24 weeks but do not develop undetectable HCV-RNA levels with treatment.[16,17]
- Treatment failure—less than 2 log IU/mL decrease in HDV RNA levels from the pretreatment baseline during treatment with PEG-IFN.[16,17]

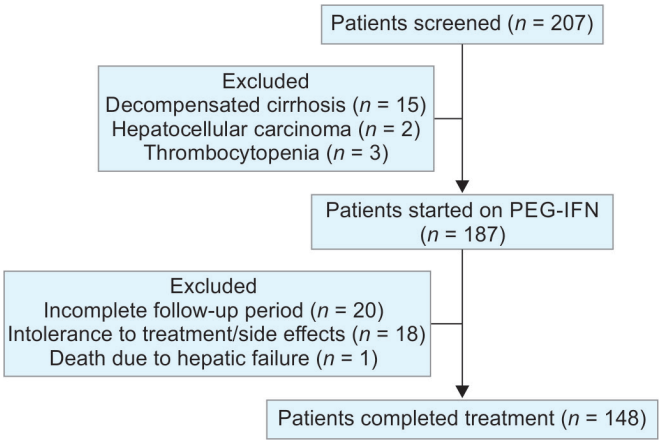

Fig. 1: Study flowchart

Statistical Analysis

Frequency (percentage) was used to report for categorical variables while quantitative variables were reported as mean ± standard deviation (SD) or median (interquartile range). Median laboratory parameters were compared within groups at 3 time points using the Friedman test and between treatment responses using the Kruskal–Wallis test. Generalized estimating equations (GEE) models were used to examine the relationships between laboratory parameters and therapy response. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported. A p-value ≤0.05 was considered statistically significant. Data analysis was performed on Statistical Package for the Social Sciences (SPSS), version 24, software.

Results

A total of 207 patients whose HCV-PCR was positive were initially inducted. Twenty patients were excluded [decompensated cirrhosis, $n = 15$; HCC, $n = 02$; and thrombocytopenia, $n = 03$ (platelet count $<70 \times 10^9$/L)] while 187 patients were found eligible to receive PEG-IFN-alfa-2a therapy. During the follow-up period of 48 weeks, 20 patients dropped out (incomplete follow-up period), 18 patients stopped therapy due to side effects, and 1 patient died (due to hepatic failure) before completing the study duration. A total of 148 patients completed the 48-week course of treatment and were considered for final analysis (Fig. 1).

There were 96 (65%) males. Their mean age was 26 ± 8.3 years. Nearly half of the patients were aged 30 years or below ($n = 68$, 46%). Other demographic characteristics are shown in Table 1. Laboratory parameters such as complete blood count and LFT were compared at three different time points: Baseline, 24 weeks, and 48 weeks. It was noted that hemoglobin ($p < 0.001$), platelets ($p = 0.013$), alanine aminotransaminase (ALT, $p < 0.001$), aspartate aminotransferase (AST, $p < 0.001$), ALP ($p < 0.001$), and total bilirubin ($p < 0.001$) showed significant within-group median differences (Table 2).

Response to the therapy was observed at 24 weeks and 48 weeks. The virological response rate was 40.5 and 32.4% at weeks 24 and 48, respectively. Partial response was seen in 24% at weeks

24 and 48. The treatment failure rate was 36 and 44% at weeks 24 and 48, respectively (Fig. 2).

A total of 29 out of 60 (48.3%) patients who had a negative PCR at week 24 remained negative at week 48, while others relapsed; 16 out of 35 (45.7%) patients who had partial response upon week 24 became PCR negative upon week 48. Three out of 53 (6%) patients who had treatment failure at week 24 achieved ETR whereas 10 (19%) out of these nonresponders achieved partial response at week 48 (Table 3). Treatment responses at week 24 and week 48 were not found to be significantly associated with each other ($p = 0.128$).

Laboratory parameters of weeks 0, 24, and 48 were compared with treatment response at 48 weeks. It was found that baseline platelets ($p = 0.009$), ALT ($p = 0.029$), AST ($p = 0.02$), and ALP ($p = 0.004$) at week 0 showed significant median differences for treatment response at week 48 (Table 4). Similarly, platelets ($p = 0.016$) and ALP ($p = 0.043$) at week 24, and hemoglobin ($p = 0.028$), WBC ($p = 0.006$), and platelets ($p = 0.028$) at 48 weeks showed significant median differences for treatment response at week 48.

For risk factor analysis using a multivariate model, a partial response was merged with a complete response and compared with the treatment failure group. The GEE model was run to assess the effect of laboratory parameters on therapy response. The multivariate model was adjusted for variables with a *p*-value below 0.250 in the univariate model. It revealed that an increase in hemoglobin (OR = 0.84, 95% CI = 0.73–0.98; $p = 0.024$) and WBC (OR = 0.84, 95% CI = 0.72–0.99, *p*-value = 0.034) with time was associated with lower risk of treatment failure. Whereas with an increase in total bilirubin (OR = 1.31, 95% CI = 1.01–1.68, $p = 0.045$), patients were more likely to have treatment failure (Table 5).

Table 1: Demographic characteristics of study participants ($n = 148$)

Characteristics	*n*	*%*
Age (years), mean ± SD, (minimum–maximum)	25.7 ± 8.3	(16–60)
Age group		
≤30	68	45.9
31–45	44	29.7
>45	36	24.3
Gender		
Male	96	64.9
Female	52	35.1
Marital status		
Single	84	56.8
Married	64	43.2
Area of residence		
Rural	59	39.9
Urban	89	60.1
Socioeconomic status		
Low class	61	41.2
Middle class	69	46.6
Upper class	18	12.2

Discussion

Hepatitis delta virus along with HBV poses a significant health threat, accelerating liver cirrhosis progression and increasing morbidity and mortality.[18] Our study highlights the demographic composition of HDV patients in Pakistan, with a substantial proportion under the age of 30. This finding, along with only 32% response rate to PEG-IFN in our study, underscores the urgency for effective therapeutic interventions in this younger demographic.

Our analysis revealed that over half of the patients were below 30 years old, corroborating the findings of Mumtaz et al. who showed a 16.6% prevalence of HDV infection and most of them belong to the same age group as ours.[19] To worsen the existing situation, more than half of them live in urban areas where education, access to knowledge, and healthcare facilities are suboptimal. As discussed in the study by Abbas Z et al., nearly two decades ago also observed a preponderance of HDV infection in young adults.[7]

The standard 48-week PEG-IFN therapy achieved a 32.4% treatment success rate in our study, slightly lower than the 42% reported by Abbas Z et al.[7] However, international literature has documented success rates as high as 82%, with these studies primarily treating HDV subspecific genotypes and incorporating oral agents alongside PEG-IFN. Additionally, some studies employed smaller sample sizes, potentially affecting the accuracy of efficacy determinations.[20–22]

Our findings also demonstrated that half of the treatment-responsive patients at 24 weeks lost their response at week 48, while nearly half of the partial responders at 24 weeks cleared their virus by week 48. Interestingly, only 5.7% of nonresponders at 24 weeks ultimately achieved viral clearance at the end of treatment. This suggests that early treatment response, whether partial or complete, increases the likelihood of response at the end of treatment. On the contrary, a lack of response at 24 weeks

Table 2: Comparison of laboratory parameters in patients receiving therapy for CHD at weeks 0, 24, and 48 ($n = 148$)

	0 week	*24 weeks*	*48 weeks*	
Laboratory parameters	*Median (Q_1–Q_3)*	*Median (Q_1–Q_3)*	*Median (Q_1–Q_3)*	*p-value**
Hemoglobin	12.8 (11.9–13.9)	13.2 (12.1–14.5)	12.0 (10.6–13.6)	**<0.001**
MCV	80.2 (66.7–87.6)	80.6 (70.2–97.4)	80.2 (64.3–95.4)	0.942
WBC	6.3 (6.1–8.3)	6.3 (6.2–8.3)	6.3 (6.1–8.3)	0.280
Platelets	201 (125–237)	212 (125–240)	200 (125–218)	**0.013**
Liver function test				
ALT	30.0 (18.2–57.0)	20.0 (15.0–26.0)	30.5 (24.0–34.0)	**<0.001**
AST	33.0 (24.0–54.0)	25.0 (19.0–34.0)	54.0 (37.5–64.0)	**<0.001**
ALP	88.0 (67.0–106.7)	77.0 (55.2–98.7)	58.0 (33.0–97.7)	**<0.001**
Total bilirubin	1.7 (1.2–2.9)	1.5 (0.9–2.1)	1.4 (0.7–2.1)	**<0.001**

**p*-value was calculated by the Friedman test. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; MCV, mean corpuscular volume; WBC, white blood cell count

predicts a low probability of treatment success. Some studies suggested HDV RNA at 24 weeks can predict the response to the treatment, giving a clue that if the treatment continuation would be beneficial or not.[21,23]

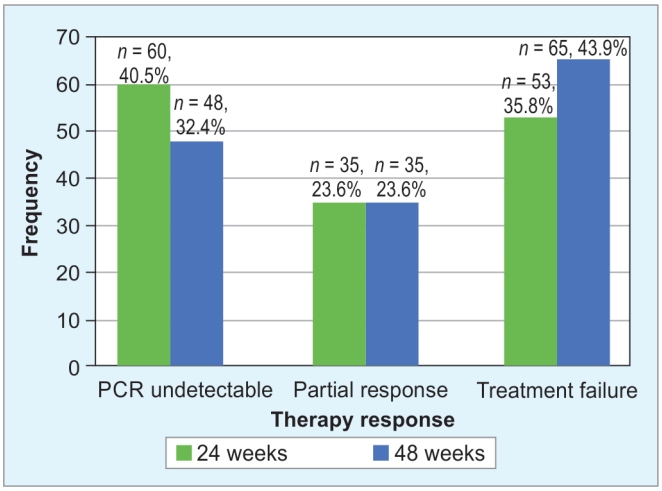

Fig. 2: Response of PEG-IFN-alfa-2a in patients with CHD at two different intervals

Table 3: Responses of patients to PEG-IFN therapy at week 24 and week 48 (n = 148)

	Therapy response at 48 weeks			
Therapy response at 24 weeks	*Total*	*PCR undetectable*	*Partial response*	*Treatment failure*
PCR undetectable	60	29 (48.3)	20 (33.3)	11 (18.3)
Partial response	35	16 (45.7)	5 (14.3)	14 (40.0)
Treatment failure	53	3 (5.7)	10 (18.9)	40 (75.5)
Total		48	35	65

n (%) are reported. *p = 0.128, calculated by McNemar test

The AST elevation could be attributed to the drug-induced effect of PEG-IFN. Conversely, alkaline phosphatase and bilirubin levels improved over the treatment course, potentially reflecting fibrosis improvement. However, this needs to be substantiated by longitudinal follow-up of these values along with other liver fibrosis parameters (FIB-4, FibroScan) during and after therapy.

A novel finding from our study is the association between treatment response and an increase in hemoglobin and WBC count. Patients with increase in hemoglobin and WBC counts had an increased likelihood of treatment response, while those with increase in total bilirubin were more prone to treatment failure. These findings, previously unreported in the literature, warrant further exploration to determine their potential utility in treatment response prediction.

Despite the less promising treatment outcomes compared to chronic hepatitis C, PEG-IFN therapy remains a viable option for CHD patients, particularly in resource-limited settings like Pakistan. The younger age of our patient population and the potential years of life saved through treatment underscores the importance of continued efforts to optimize CHD management. Further studies investigating hemoglobin and WBC count as treatment response predictors are warranted. While PEG-IFN therapy exhibits limitations, the development of newer, more effective therapies for CHD is eagerly anticipated.

Although our study encompasses a larger patient cohort than any other from our region, further research involving a broader patient population is necessary. Additionally, separate analyses of patients with and without cirrhosis would provide valuable insights into the differential therapeutic responses and adverse effects of PEG-IFN in these subgroups. A larger cohort would also enable us to determine the significance of the response-predicting variables identified in our study and explore the feasibility of developing a pretreatment predictive score.

Table 4: Comparison of laboratory parameters in patients by therapy response for CHD (n = 148)

	Therapy response at 48 weeks			
Laboratory parameters	*PCR undetectable*	*Partial response*	*Treatment failure*	*p-value**
Parameters at week 0				
Hemoglobin	12.4 (11.5–14.3)	12.9 (12.3–13.6)	12.6 (11.9–14.1)	0.390
MCV	80.0 (70.2–90.0)	80.2 (60.2–87.6)	80.6 (68.5–89.3)	0.545
WBC	6.2 (5.9–8.2)	6.3 (6.2–8.2)	6.4 (6.1–8.7)	0.337
Platelets	200.5 (105.0–227.5)	218.0 (199.0–300.0)	178.0 (105.0–217.0)	**0.009**
ALT	38.5 (17.5–63.0)	23.0 (16.0–30.0)	34.0 (20.0–58.0)	**0.029**
AST	44.0 (24.5–66.5)	26.0 (22.0–34.0)	34.0 (22.0–8.0)	**0.020**
ALP	98.0 (74.2–109.0)	72.0 (48.0–91.0)	95.0 (71.0–106.5)	**0.004**
Total bilirubin	1.7 (1.4–2.9)	1.5 (1.0–2.4)	2.0 (1.1–3.2)	0.253
Parameters at week 24				
Hemoglobin	13.1 (12.1–14.5)	12.9 (12.1–13.6)	13.6 (12.1–14.6)	0.662
MCV	80.6 (70.2–100.5)	79.8 (60.2–87.6)	80.6 (70.2–100.5)	0.343
WBC	6.3 (6.1–8.2)	6.3 (6.2–8.2)	6.3 (6.2–8.2)	0.855
Platelets	214.5 (121.2–246.7)	218.0 (200.0–300.0)	200.0 (120.0–218.0)	**0.016**
ALT	19.0 (15.0–24.7)	20.0 (16.0–27.0)	20.0 (15.0–28.0)	0.725
AST	26.0 (21.0–44.0)	25.0 (21.0–33.0)	24.0 (15.0–34.5)	0.307
ALP	82.5 (60.5–101.7)	68.0 (48.0–87.0)	81.0 (56.5–98.5)	**0.043**
Total bilirubin	1.6 (1.0–2.3)	1.5 (0.9–2.4)	1.4 (0.9–1.9)	0.267

(Contd...)

Table 4: *(Contd...)*

	Therapy response at 48 weeks			
Laboratory parameters	*PCR undetectable*	*Partial response*	*Treatment failure*	*p-value**
Parameters at week 48				
Hemoglobin	11.6 (10.5–13.4)	11.6 (9.7–13.4)	12.6 (11.6–13.6)	**0.028**
MCV	78.2 (60.0–87.6)	80.9 (59.2–98.6)	80.6 (65.4–91.5)	0.399
WBC	6.3 (6.2–8.3)	6.2 (6.1–6.3)	6.3 (6.2–8.3)	**0.006**
Platelets	210.0 (129.7–217.5)	200.0 (120.0–216.0)	200.0 (109.0–220.0)	0.715
ALT	32.5 (26.5–39.0)	26.0 (24.0–32.0)	30.0 (24.0–34.0)	**0.028**
AST	57.0 (33.2–65.7)	54.0 (45.0–64.0)	52.0 (35.0–61.0)	0.360
ALP	70.5 (32.2–98.0)	57.0 (34.0–97.0)	54.0 (33.0–97.5)	0.929
Total bilirubin	1.5 (1.0–2.1)	0.9 (0.5–2.1)	1.4 (0.4–1.6)	0.056

Median (Q_1–Q_3) are reported. **p*-value was calculated by the Kruskal–Wallis test. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; MCV, mean corpuscular volume, WBC, white blood cell count

Table 5: Risk factors associated with therapy response of treatment failure based on GEE model

	Treatment failure vs partial response/PCR undetectable			
	Univariate		*Multivariate*	
Characteristics	*OR (95% CI)*	*p-value*	*OR (95% CI)*	*p-value*
Hemoglobin	0.86 (0.74–0.99)	0.032	0.84 (0.73–0.98)	0.024
MCV	1.00 (0.99–1.01)	0.911	–	
WBC	0.86 (0.73–1.01)	0.062	0.84 (0.72–0.99)	0.034
Platelets	1.00 (0.99–1.01)	0.418	–	
ALT	0.98 (0.96–1.01)	0.202	0.98 (0.96–1.00)	0.125
AST	1.00 (0.99–1.01)	0.428	–	
ALP	1.00 (0.99–1.01)	0.547	–	
Total bilirubin	1.28 (0.99–1.64)	0.054	1.31 (1.01–1.68)	0.045

Adjusted for those variables whose *p*-values were less than 0.25 in the univariate model. CI, confidence interval; GEE, generalized estimating equations; OR, odds ratio

Conclusion

It is noted that PEG-IFN therapy remains as a viable treatment among patients with CHD, despite its limitations. The urgent need for effective alternative therapies for CHD patients is evident.

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