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HEPATITIS D TREATMENT WITH PEGYLATED INTERFERON: OUTCOME ASKING FOR AN URGENT ALTERNATIVE.

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ABSTRACT:

BACKGROUND: Viral hepatitis is a global health issue mainly prevalent in countries in Asia and Africa where hepatitis B (HBV) is endemic. **OBJECTIVE:** To determine the efficacy of pegylated interferon alpha in Hepatitis D patients. **STUDY DESIGN:** Quasi-experimental study. **PLACE AND DURATION OF STUDY:** Al-Tibri Medical College Hospital Karachi and OPD Saylani Welfare Trust Karachi from August 2021 to December 2022. **METHODOLOGY:** Adult patients of either gender and all ages infected with HDV as evidenced by anti-HDV antibodies positive along with detectable levels of HDV RNA in the serum by polymerase chain reaction (PCR) were included in the study. A written informed consent was taken from all patients, and pegylated interferon alpha (180 mcg subcutaneously weekly) was started for at 48 weeks. HDV RNA by quantitative PCR has been done before and after treatment. All patients were followed up in the outpatient clinics every month for clinical, hematological, and biochemical assessments for any adverse effects of treatment. At the end of treatment, the overall response to therapy as depicted by non-detectable HDV RNA by PCR was analyzed by applying the chi-square test and using SPSS 23.0 statistical software. Significance was kept at a p-value of less than 0.05. **RESULTS:** Ninety-seven patients were assessed for eligibility. After excluding 31 patients, a total of 66 patients were enrolled for a 48-week course of pegylated interferon therapy at a dose of 180 mg/week. Out of the 42 patients, 16 (38.1%) responded to the treatment, compared to 26 (61.9%) no responders. No significant difference was seen in association with gender, age and viral load of patients with responders and non-responder's groups of treatment. **CONCLUSION:** The study found that pegylated interferon treatment of hepatitis D patients was challenging, with only 38% of patients achieving sustained suppression of hepatitis D virus replication after 48 weeks of treatment.

KEY WORDS: Hepatitis D. Pegylated interferon alpha. Polymerase Chain Reaction.

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INTRODUCTION

Viral hepatitis is a global health issue mainly prevalent in countries in Asia and Africa where hepatitis B (HBV) is endemic. Among those viruses, the Hepatitis D virus (HDV) has always remained a challenge for any healthcare system in the world due to reasons like the unknown exact burden of disease, the unavailability of vaccines, and inadequate or limited treatment options. But as HDV can only infect patients who are already infected with the hepatitis B virus (HBV) and results in an exacerbation of their disease, [1] its infection can be prevented indirectly by using the HBV vaccine to fend off hepatitis B.

Worldwide, about 0.16% (0.11–0.25) of the general population, totaling 12.0 (8.7–18.7) million people, are estimated to be anti-HDV positive. [2] Hotspots have been reported in Vietnam [3] and Yakutia. [4] In recent years, the prevalence of HDV has declined in different parts of the world, especially Europe, and the vital reasons for this downturn are the extensive universal HBV vaccination and improvements in socioeconomic conditions. [5] In contrast to this, HDV infection is still prevalent in some countries, including Pakistan, [6] where prevalence has been reported as higher and widely variable (16–27%). [1] In general, 30–50% [7] of HBsAg positive patients are seropositive for HDV, but there is a well-defined area in the middle of the country, so-called the "Delta Belt." Countrywide, the HDV RNA positivity rate was 28% in 2011 in HBV viremia patients, [8] while a metropole city of the country, Karachi, also has almost the same situation of anti-HD being found in 28.1% of HBsAg positive patients. [9]

In regard to transmission, HDV is transmitted almost exactly in the same way as HBV. The routes of transmission include perinatal, sexual, and percutaneous transmission, like IV drug abuse. But in countries like Pakistan, where viral hepatitis is endemic, percutaneous transmission through reused syringes and needles is also an important mode of transmission of both HBV and HDV. [10]

Until now, the only available treatment option for hepatitis D has been pegylated interferon alpha (PEG-IFN), which achieves sustained suppression of HDV replication in only 25% of patients, [11] and nucleotide analogs (NUCs) are ineffective against HDV. [12] Hence, we don't have options or grounds to fight against this lethal virus. This situation makes HDV a great threat to the world's health system, creating a situation like war without weapons.

To our knowledge, so far no local study has been done to assess the response rate of the only available PEG-IFN therapy against HDV without HBV active replication. This study was planned to evaluate the treatment response and its related factors against HDV in our local population.

PATIENTS AND METHODS:

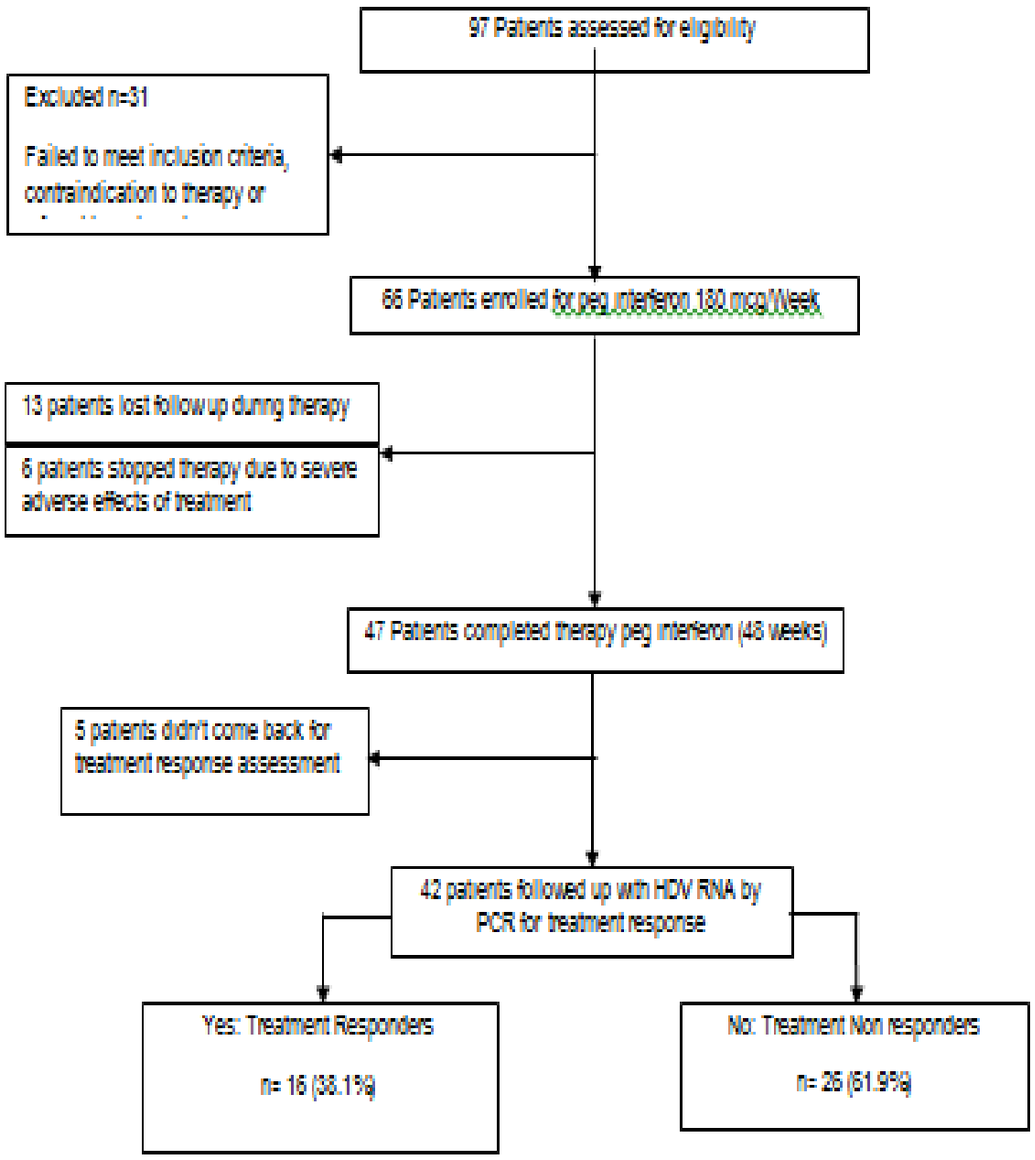
This quasi-experimental study was carried out at the Department of Medicine, Al Tibri Medical College & Hospital Karachi, and the hepatitis OPD at Saylani Welfare Trust, Karachi, from August 2021 to December 2022. After obtaining Institutional ethical approval all adult patients, either gender, with HBsAg positive were screened for Hepatitis D with anti-HDV antibodies. In the case of a positive screening test for HDV as well, patients were assessed for active viral replication of both viruses by polymerase chain reaction (PCR), that is, HBV DNA and HDV RNA (quantitative/viral load). Following the mentioned viral workup, patients were categorized according to the results of PCR; only HDV RNA detectable patients were evaluated clinically as well as by laboratory investigations for eligibility for specific treatment with PEG-IFN and included in this study, while HBV DNA alone or in combination with HDV RNA detectable (dual viral infection) were excluded from this study, but specific treatments were advised to them accordingly.

Patients were excluded from the study if there was evidence of decompensated cirrhosis, patients with a coinfection of HIV, HBV, or HCV infection, previous organ transplantation, or patients with contraindications to PEG-IFN like psychiatric disease, seizure disorder, or serious cardiovascular disease. Decompensated cirrhosis is evaluated clinically and with other parameters like an abdominal ultrasound, upper GI endoscopy, and liver biopsy in suspected cases where needed. In suspected cases, the presence of antinuclear antibodies (ANA) was checked to exclude autoimmune hepatitis.

After informed consent, PEG-IFN (180 mcg subcutaneously weekly) was given to patients for at least 48 weeks. HDV RNA by

quantitative PCR has been done before for eligibility and after treatment for the response at 48 weeks. All patients were followed-up in the outpatient clinics every month until treatment was completed and assessed clinically along with a hematological and biochemical assessment on each follow-up visit for any adverse effects of treatment. At the end of treatment, the overall response to therapy as depicted by non-detectable HDV RNA by PCR was analyzed by applying the chi-square test and using SPSS 23.0 statistical software. Significance was kept at a p-value of less than 0.05.

Figure I. Study diagram shows virologic response rate in hepatitis D patients after treatment with pegylated interferon for 48 weeks.



DATA ANALYSIS:

The analyses were performed using Statistical Packages for Social Sciences (SPSS 23). For categorical variables, frequency and percentage were used. The chi-square test of independence was used for data analysis of responders and non-responder's groups. A P- value of 0.05 was considered statistically significant.

RESULTS:

The number of study participants and the patient's status were shown in Figure I. The eligibility of 97 patients was evaluated. The study eliminated a total of 31 patient samples because they either did not match the inclusion criteria (n = 24), had therapeutic contraindications (n = 4), or did not want to participate (n = 3). A total of 66 patients were enrolled in a 48-week course of pegylated interferon therapy at a dose of

180 mg/week. Only 42 of the 47 patients who received therapy for the full 48 weeks returned for a treatment response evaluation. Out of the 42 patients, 16 (38.1%) responded to the treatment, compared to 26 (61.9%) who did not. Out of 42 enrolled patients, 27 (64.2%) were males and 15 (35.8%) were females. The mean age was 28.38 years.

Table I presented the characteristics that include age, gender, HDV viral loads, and ALT of the treatment responders and non-responders' groups of patients and showed non statistical significant differences in both of these groups.

The side effects reported by these patients were usually PEG-IFN-related and included fatigue, fever, and headache. These side effects did not require a dose reduction. The hematological responses that were reported in this study were leukopenia and anemia. There is a statistically significant p- value of 0.022 found in leukopenia in treatment responders and non-responders groups, as shown in Table II.

Table I. Base line characteristics of treatment responder and non-responder patients(n=42)

Characteristics	Total (n=42)	Responders	Non-Responders	p-value
Gender				
Male	27	10 (40%)	17 (60%)	0.850
Female	15	06 (37%)	09 (63%)	
Age (years)				
<20	08	03 (37.5%)	05 (62%)	0.273
21-40	30	10 (33.3%)	20 (66.7%)	
>40	04	03 (75%)	01 (25%)	
HDV Viral load (IU/mL)				
<10000	05	02 (40%)	03 (60%)	0.563
10001-50000	09	04 (44.4%)	05 (55.6%)	
50001-100000	03	00	03 (100%)	
>100000	25	10 (40%)	15 (60%)	
ALT (IU/L)				
<40	02	01 (50%)	01 (50%)	
41-80	14	07 50%)	07 (50%)	0.633
81-120	08	02 (25%)	06 (75%)	
>120	18	06 (33.3%)	12 (66.7%)	

Table II. Adverse effects profile of therapy in responders and non-responders (n=42)

Adverse effects	Responders	Non-Responders	p-value
Fatigue			
Yes 31 (73.8%)	12 (38.7%)	19 (61.3%)	0.891
No 11 (26.2%)	04 (36.4%)	07 (63.6%)	
Fever			
Yes 17 (40.5%)	06 (35.3%)	11 (64.7%)	0.758
No 25 (59.5%)	10 (40%)	15 (60%)	
Headache			
Yes 11 (26.2%)	04 (36.4%)	07 (63.6%)	0.891
No 31 (73.8%)	12 (38.7%)	19 (61.3%)	
Anemia			
Yes 06 (14.3%)	01 (16.7%)	05 (83.3%)	0.243
No 36 (85.7%)	15 (41.7%)	21 (58.3%)	
Leukopenia			
Yes 03 (7.1%)	03 (100%)	00	0.022*
No 39 (92.9%)	13 (33.3%)	26 (66.7%)	

DISCUSSION

In Pakistan, the HBsAg positive rate in HDV individuals' ranges from 14 to 18%, and it rises to 37 to 38% in patients with HBsAg positive chronic liver disease. [13] PEG IFN is the only available treatment option in Pakistan. There is presently no authorized regimen for individuals with chronic HDV infection, making therapy difficult. The 25% of the individuals treated with PEG IFN achieved a virological response in 24 weeks. [14] Even though they exhibited a viral response 24 weeks after treatment, patients who received a one-year course of PEG IFN over a long period showed delayed HDV-RNA relapse in more than 50% of instances. [15]

The surprising incidence of HDV in this study compared to the Brazilian study [16] could be due to the fact that our study patients were from the low socioeconomic status of Sindh and Baluchistan and were isolated HDV patients without active replication of HBV. However, the previous studies reported a 23.6% incidence in Larkana and were conducted in 2008–2011. [17] The previous study from Pakistan also reported a high incidence in the rural communities of Sindh and Baluchistan. [18] The diversity present could be due to active preventive measures not being taken due to low literacy rates. The incidence rates differ in various cities of India, like Madhya Pradesh (2%), West Gujarat (8.5%), and Mumbai (16%), with HBV DNA positive samples in HBsAg. [19]

Our study showed a high incidence in males compared to females. Even for minor complaints, numerous injections and intravenous drips are often used, which may be the cause. Previous studies in Pakistan also found greater proportions of hepatitis D virus infection in men. [17] However, one study from Nigeria, Africa, found the opposite outcome in favor of women who underwent female circumcision and received injections from non-certified healthcare practitioners. [20]

In this study, the incidence was more prevalent in younger adults. Previous studies from Pakistan [13] and Brazil [16] have also established higher rates of HDV infection among young adults, suggesting sexual transmission is the main cause. The routine uses of tainted needles, therapeutic injections and drips, infected instruments, and barbers recycling old-fashioned razors could be other factors that were more prevalent in young patients in HDV.

The HDV treatment response failure was high in this study as the patients were not active cases of hepatitis B replication, and most of the patients were referred from the rural community to the charity hospital for treatment. According to previous studies, genotype plays a role in the suppression of HBV replication in chronic hepatitis D patients. Individuals with HBV genotype A infections show stronger evidence of viral replication inhibition than individuals with HBV-D or E infections. [21] This is in contrast to research where patients were only monitored for 24 weeks following treatment and a sustained response rate of 23% was discovered. This may be because of variations in genotype and viral load, a prompt virological response, the grade of fibrosis, and the extent of the disease. [22]

In this study, treatment failure was more prevalent in males compared to females. While gender itself may not be a direct factor influencing treatment failure, However, hormonal differences between genders could potentially influence immune responses and the efficacy of antiviral treatments, and more research is needed to fully understand the potential impact of gender on hepatitis D treatment outcomes. The synergistic action of male and female sex hormones, immunological responses, and viral components causes a gender discrepancy in the course and outcome of hepatitis virus infection. [23]

In this study, ALT did not find any relationship between responders and non-responder patients with interferon therapy. This is contrary to a study that showed normalization of ALT in a significant number of patients treated with pegylated interferon even without a virological response. [22] Ideal treatment end points in HDV treatment is sustained virological response (SVR) as evidenced by undetectable HDV RNA after 24 weeks of treatment completion. Hercun and colleagues reported patients had undetectable HDV RNA in serum at 8 years of treatment and follow-up, and the sample size in this study was too small. [24] Our study couldn't assess SVR due to loss of follow up by majority of patients.

In PEG IFN studies for chronic hepatitis D, undetectable HDV RNA was regarded as proof of a sustained virological response (SVR) and a successful course of treatment six months after the completion of treatment. In order to sustain the likelihood of a clinical benefit, the HDV-RNA levels at the conclusion of therapy can be maintained after treatment termination or the treatment can be continued for a lengthy period of time. However, the affordability, efficacy,

and safety of the drugs used will determine the practicality of long-term treatment. Therefore, there is a time to have HBsAg loss after using the combination therapy of INF with new drugs that are under trial. [25]

Limitations of the study:

There were a few limitations of the study: first, the genotyping of HDV could not be carried out, which might be the main factor for treatment response prediction; second, the long term follow up could not be performed for assessment of exact SVR, and last but not least, the liver biopsy (histopathology) was not performed in all cases to determine the stage of fibrosis.

CONCLUSION

The study found that PEG IFN treatment of hepatitis D patients was challenging, with only 38% of patients achieving sustained suppression of hepatitis D virus replication after 48 weeks of treatment. There was no statistically significant difference present between age, gender, viral load, and biochemical enzymes in responders and non-responder groups. There is an urgent need for new treatment strategies for the sustained virological response in Pakistan to provide hope for the future.

ETHICS APPROVAL: The ERC gave ethical review approval.

CONSENT TO PARTICIPATE: written and verbal consent was taken from subjects and next of kin.

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CONFLICT OF INTEREST: No competing interest declared.

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