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Pegylated Interferon-Lambda in Chronic Hepatitis D Virus Infection: A Phase II Randomized Trial: Clinical Evaluation

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Abstract
HDV is an uncommon, but a severe condition of the liver that has few treatment options. The safety and efficacy of pegylated interferon-lambda (PEG-IFN-lambda) were compared to that of pegylated interferon-alpha (PEG-IFN-alpha) in patients (n=64) with HDV in this Phase II randomized controlled trial. Participants were injected subcutaneously to receive injections on a weekly basis over 48 weeks. Primary outcomes were overall virological response and ALT normalization whereas tolerability was the targeted secondary outcome. Statistically significant results included a 42 percent virological suppression percentage in the PEG-IFN-A arm compared to 21 percent in PEG-IFN-Lambda) with a significantly reduced flu-like symptoms and hematologic toxicity in the PEG-IFN-Lambda arm. PEG-IFN-lambda patients experienced the normalization of the ALT in 39 percent of patients. This result enhances the use of PEG-IFN-lambda as a potential treatment strategy since long-term validation is critical as further Phase III studies are required.

Keywords: ***Hepatitis D virus, pegylated inter-feron-lambda, pegylated inter-feron-alpha, chronic infection, virological response, ALT normalization, phase II trial, tolerability.***

1. Introduction

1.1 Burden of Chronic Hepatitis D Virus Infection and Unmet Therapeutic Need

Chronic hepatitis D virus (HDV) infection is an acute entity with a serious clinical weakness that exclusively occurs in patients that are infected with hepatitis B virus (HBV). HDV is the highest virulent virus hepatitis and needs the existence of HBV in its replication. The disease commonly causes an insidious hepatic pathology including liver failure, cirrhosis and hepatocellular carcinoma, which is among the most disastrous sources of liver-related morbidities and mortality terrestrially.

The worldwide burden of HDV infection is estimated as 510 percent of the population with chronic HBV infection, although it may be greater than this because of underrecognition, especially in sub-Saharan Africa, Eastern Europe, and other parts of Asia, where HBV is endemic. In the industrialized nations, the disease can be underreported, and thereby leading to untreated cases as patients do not get a diagnosis until considerable liver deterioration has reached. This is further complicated by the fact that chronic HDV infection has a more aggressive course as compared to chronic HBV alone and a large portion of patients develop cirrhosis within twenty years of infection.

At present, the treatment possibilities of HDV are extremely scarce. Pegylated interferon alpha (PEG-IFN-alpha) is the standard of care, but its performance is unsatisfactorily suboptimal as the response rates are usually lower than 30 percent. Moreover, PEG-IFN-a is characterized by severe adverse reactions consisting of flu-like symptoms, hemocytological toxicity and neuropsychiatric complications that have all the deleterious effects of patient adherence and quality of life. These shortcomings emphasize the necessity in finding more effective and well-tolerated treatments to chronic HDV infection.(1)

With the heavy impact HDV infection has and the absence of effective and nontoxic treatment, there is an evident unmet need in treatment, and it is a necessity to find a class of antiviral agents with a better efficacy, safety and the capability of managing the disease in the long run.

1.2 Pegylated Interferon-Lambda: Rationale to Use as an Alternative Therapy

PEG-IFN-lambda is an emerging novel potential medicine that could be used to treat chronic HDV infection as a replacement to PEG-IFN-alpha. Interferon-lambda (IFN-lambda) is a type III interferon which exhibits significant overlap in antiviral activity with interferon-alpha but agonist activity at an alternative receptor, the interleukin-28 receptor (IL-28R) rather than at the interferon-alpha receptor. This difference is important since it gives rise to a more selective immunological reaction, and this is expected to have reduced side effects, particularly, flu like symptoms and hematologic toxicities which are often seen in PEG-IFN- alpha.

Preclinical models have confirmed that PEG-IFN-l has a strong set of antiviral qualities against a set of viruses including viral illnesses, such as hepatitis B and C. The feasibility of PEG-IFN-lambda in HDV infection is that this has the ability to target more specifically the liver making side effects of PEG-IFN-alpha less of a problem systematically. Moreover, new emerging evidence indicates that PEG-IFN-l can induce a more potent immune reaction even in patients with a chronic viral infection by improving viral clearance and immune modulation.

PEG-IFN-lambda has the potential to be a better tolerable treatment option than PEG-IFN-alpha; this is based on the fact that PEG-IFN-lambda has a good safety profile in studies in animal models and pre-clinical trials in early clinical study. These properties render PEG-IFN-l as a prospective treatment against chronic HDV notably in those individuals who do not respond or those that react adversely to PEG- IFN-alpha therapy.(2)

Moreover, this application of PEG-IFN-lambda may produce a more focal immune response with a decreased propensity to the systemic side effects typically found with systemic immune modulation, namely those of the more classic interferons. These advantages together with the possibility of attaining similar or better virological suppressions rates justify the investigations into PEG-IFN-lambda as an alternative treatment of chronic HDV infection.

1.3 The objectives of carrying out such a phase II randomized controlled trial are as follows.

The major goal of this Phase II randomized controlled trial was to compare the safety and efficacy of PEG-IFN- l in patients with chronic HDV infection to the current standard of care, PEG-IFN-a and compare the efficacy level. In particular, it was expected that the study would determine the virological response rates, i.e., the magnitude of the HDV RNA reduction at 2-log level, and the normalization of the alanine aminotransferaser (ALT) levels, a liver inflammation and damage indicator.

Secondary goals were assessment of tolerability and safety of both treatments. This included surveillance of the adverse events especially flu-like symptoms and the hematologic toxicities typically seen with interferon based products. The study was intended to understand whether PEG-IFN- an alternative to PEG-IFN- had a better safety record and would also exert similar antiviral effects

A secondary objective was to investigate the possibilities of PEG-IFN- application to cause sustained virological responses, which would essentially be an important milestone in providing long-term HDV infection control. Due to the absence of effective treatment and a high load of HDV cases, this trial was conducted to provide data that would inform future Phase III trials that could provide the field with a new standard of care in the treatment of chronic HDV infection using PEG-IFN-l.

The overall goal of this Phase II trial was to support initial evidence of efficacy, safety, and tolerability of PEG-IFN- l to prepare the way to future, larger trials to establish its use in the management of HDV chronic illness and potentially fill a gap in therapeutic initiatives in HDV patients.(3)

2. Design and Methodology Trials

2.1 Randomization Strategy and the study population characteristics

The goal of this phase II randomized controlled trial (RCT) was to determine the safety and efficacy of pegylated interferon-lambda 1 (PEG-IFN-lambda 1)versus pegylated interferon-alpha (PEG-IFN-alpha) in the treatment of chronic hepatitis D virus (HDV) infection. The protocol of the study was of high ethical standards and adopted by suitable institutional review boards. A sample of 64 individuals, who have chronic HDV infection, and satisfy the predetermined inclusion criteria was recruited in several centers.

The inclusion criteria were all adults, aged 18 to 65 years and chronically infected with HDV as defined by detectable HDV RNA in serum and persistent elevated levels of alanine aminotransferase (ALT), reflecting continued liver inflammation. All participants were co-infected with hepatitis B virus (HBV) because HDV cannot reactive unless HBV is available. Exclusion included individuals with decompensated cirrhosis, other active endemias, serious comorbid conditions, or previous therapies with treatments that included interferon.

The randomization of participants was done in a ratio of 1:1 to either the PEG-IFN-lambda arm or the PEG-alpha arm using computer-generated randomization scheme. This managed to provide an objective distribution of participants in the treatment arms. To reduce potential confounders, stratified randomization was conducted based on the Child-Pugh score and the MELD (Model for End-Stage Liver Disease) score as measures of severity of baseline liver disease. The experiment had concealment of allocation to eliminate bias in treatment administration and outcome evaluation by keeping participants and investigators in the blind treatment assignment condition.

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Baseline characteristics of the two arms were well balanced with regard to age, gender, body mass index (BMI), HDV RNA level, ALT level, and stage of the liver disease (Table 1). The average age of the participants was about 45 years and the gender was composed of an equal number of males and females. Most patients suffered moderate liver disease and baseline HDV RNA was 5 7 log IU/mL. These properties allowed deriving a representative sample of patients with chronic HDV infection that could represent a scenario in the real clinical practice.(4)

2.2 PEG-IFN-lambda and PEG-IFN-alpha Intervention Arms and Dosing On-therapy Dose Reduction Dose Escalation

This was a prospective trial that incorporated two treatment arms through which one group of patients received PEG-IFN- L and the other received PEG-INF-a. Both arms had a similar treatment consisting of weekly subcutaneous injections over a 48 week time period. The schedules and the pharmaceutical forms of dosing were as follows:

PEG-IFN-lambda arm: On this arm the patients were treated to 180 μg of PEG-IFN-lambda given as a subcutaneous injection once in a period of 7 days and was done on a total of 48 weeks. PEG-IFN-lambda is an office pegylated interferon-lambda that has been modified to increase its half-life and allow once-a-week delivery. The increased molecular weight and pegylation decrease the rate of injections with no loss of efficacy against antivirus.

PEG-IFN-α arm: The subjects got 180 mu of PEG-IFN-alpha once a week, 48 weeks on the contrast group. PEG-IFN-alpha is the currently standard of care to chronic HDV infection, and its dosing pattern was in accordance to clinical recommendations.

Both treatments were provided by the qualified medical personnel, and the patients were observed frequently to report adverse effects and determine whether they were experiencing any side effects of treatment. The treatment length (48 weeks) was selected and understood due to the available clinical experience with interferon based regimens which have long durations in providing ideal virus suppression in chronic viral infections.

Compliance and adverse events were the very close results of both the treatment arms. In the event of serious adverse reactions, employees could reduce doses and/or temporarily stop treatment, following mechanisms suggested by the protocol. At service during the 48 weeks of treatment, the patients were tracked further, 24 weeks to assess sustained BMs and long-term safety.(5)

2.3 Primary and Secondary Endpoints having specified Response Criteria

The choice of primary and secondary endpoints of the trial is a key to acquiring a full picture of the efficacy and safety of PEG-IFN-lambda in comparison with PEG- IFN-alpha. The boundaries of these endpoints were established at the beginning of the research to guarantee that the paperwork is clear and measurable.

Primary Endpoints:

- Virological Response: Virological response was the is primary measure of efficacy and was based on the percentage of patients with a 2-log or greater reduction in HDV RNA at week 48 compared to baseline. Virological response indicates the viral suppression and reflects the success of the treatment due to the antiviral quantity of it. This endpoint is regarded as a clinically significant endpoint, because it is correlated with less development of the disease and possible improvements in the liver functions.
- The Secondary primary endpoint was the normalization of lanine aminotransferase (ALT) is an important biomarker of inflammation of the liver. Normalization of ALT was set as ALT values within the normal reference range (<40 U/L), confirmed at week 48. ALT correction is a key clinical indicator of liver health, which means that one has lowered liver damage and inflammation.

Secondary Endpoints:

- Tolerability and Safety: As such adjunctive endpoints involved the analysis of adverse effects with an emphasis on flu-like effects, hematologic side effects (e.g., neutropenia, thrombocytopenia), and neuropsychiatric side effects (e.g., depression, fatigue). Adverse events were classified based on the severity and frequency of occurrence with a precise monitoring during the period of trial life.
- Sustained Virological Response (SVR): A sustained virological response was defined that no HDV RNA could be detected in blood 24 weeks after the end of therapy (week 72). This secondary endpoint measures the durability of the antiviral efficacy and is a long-term treatment success defining factor.
- Quality of Life (QoL): Quality of life was examined as the secondary outcome measure with the use of SF-36 questionnaire at the end of the treatment course to determine how a patient feels after its

completion. This was critical in terms of capturing evidence of tolerability of the treatments on the basis of their impact on daily functioning and emotional well-being.

All of these endpoints were analyzed with both intention-to-treat (ITT) and per-protocol (PP) using a p-value of <0.05 as defining statistical significance.(6)

3. Enrolment of patients into the trial and their baseline characteristics

3.1 Eligibility Criteria

The eligibility criteria put in place in this Phase II randomized controlled trial was well formulated to offer potential benefits to patients with chronic hepatitis D virus (HDV) infection and to ensure their safety. Inclusion criteria were:

- Age: Participants had to be between 18 and 65 years of age in order to ensure that study population was of adults with chronic infection with HDV.
- Diagnosis of Chronic HDV Infection: The patients should have a chronicle HDV infection as evidenced by HDV RNA stability in serum at least 6 months and HBsAg positivity.
- Liver Function: Elevated liver enzymes (alanine aminotransferase; ALT greater than 40 U/L) were a key inclusion criterion in the study as this was an indicator of liver inflammatory disease process.
- HBV Co-infection: All patients were co-infected with hep B virus (HBV), because HDV can not replicate without HBV.
- Liver Disease Stage: The enrolment criteria was patients with moderate level of liver disease (without cirrhosis or with compensated cirrhosis) assessed clinically and by use of non-invasive evaluation systems such as Child-Pugh score and liver stiffness.

Exclusion criteria allowed including individuals who:

- Decompensated Cirrhosis: Patients with advanced liver disease (Child-Pugh classB or C) or a MELD (Model for End-Stage Liver Disease) score above 15 were excluded by virtue of potential complications being severe.
- Other Active Infections: Patients with active infections like HIV, hepatitis C among others known at any given time would not be eligible to enroll.
- Prior interferons therapy: Patients with prior experience of any other interferon-based therapies such as PEG-IFN-alpha or PEG-IFN-lambda as a previous treatment have been excluded to avoid bias and complications.
- Pregnancy and Lactation: Pregnant women, breast feeding females, or women planning to become pregnant during the trial were excluded as the trial interventions were likely to affect the condition of the mothers negatively.

These eligibility criteria were implemented to make sure participants receive the investigational treatments with well-characterized diagnosis of chronic HDV and received a certain stage of liver disease where the study results may be of meaning.(7)

3.2 Results on Demographic and Clinical Characteristics of the Participants Enrolled

The trial was half-randomized with 64 patients, with each arm receiving either 1-PI (PEG-IFN- a) (n=32) or 2-PI (PEG-IFN- l) (n=32). The demographic and clinical baseline variables between the participants who were enrolled by the newly dispensing physician and the existing physician are comparable, which assures that they have no significant difference that can influence the outcome of the comparative study.

Age: the average age of the participants was 45 years of age, and the age range of the subjects covered 18-65 years. The demographics (age distribution) were similarly distributed under both arms of treatment and the difference between the mean age was not significant.

The distribution of gender was balanced in the two arms. Four out of 64 patients were females and six out of 64 patients were males, which is representative of gender distribution of chronic hepatitis B and D injectors.

Ethnicity: The participants were more representative of patients that live in parts of the world where HBV and HDV are more endemic, including South Asia, Eastern Europe and parts of Africa. This represents the world prevalence of HDV and is applicable to a large number of people.

Body Mass Index (BMI): The average BMI value of the participants was 26.5kgm/m 2 and the majority of the participants had a normal to overweight BMIs (18.5-29.9kgm/m 2).

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These baseline demographic traits show that the study population was not selective but representative of most patients with chronic HDV infection; therefore, there was generalizability of the study results to a real-life clinical condition.(8)

3.3 Baseline Viral Load and Liver Function Markers Distribution

At baseline, viral load and liver functions markers distribution were similar among the two groups of participants, and there were no significant differences between them.

The Aspartate Levels: The baseline aspartate level counts were between 5.0 and 7.0 log IU/mL, which falls in-line with moderate to high viral replication of HDV. Average pre-treatment HDV RNA was 6.2 logs IU/mL in the two treatment arms. The fact that the participants were infected and indeed had active infection suggests that they could be subjected to antiviral intervention.

Alanine Aminotransferase (ALT): Mean ALT value was 110 U/L and the range was 40-200 U/L. Raised ALT in the patients with the chronic HDV infection indicates that there is inflammation of the liver tissue and this is the usual state in such patients. The ALT levels of the PEG-IFN-a arms and the PEG-IFN-l arms were not significantly differing.

HBsAg: All participants were positive to HBsAg, meaning that they were chronically infected with hepatitis B. The viral load was also well-controlled since the average HBsAg level was 3.5 log IU/mL in both groups, and thus, reflected the stable infection status of hepatitis B virus.

Liver Function Tests: Most of the participants had normal liver functions (reflected by bilirubin and albumin level) indicating the normal liver functioning in the study population. Yet mild liver disease was noted in some of our patients which correlated with moderate liver disease in HDV infection.(9)

These baseline parameters gave a clear idea of how severe the liver disease was in the patients and the level of viral load, establishing the benchmark on which the approach of the interventions would be measured to see the level of reduction of HDV RNA, liver function, and ALT normalization. The similarity of baseline characteristics of the two treatment arms made it possible to assume that all the differences in clinical outcomes could be explained by the chosen form of treatment.

4. Virlogical and biochemical Results

4.1 Virological Rates of Suppression and Statistical Significance

The main efficacy outcome of this Phase II randomized controlled trial was virological response that was measured at week 48 as a 2 log reduction in HDV RNA compared with baseline. Virological suppression rates were reported to be significantly larger in the PEG-IFN-la group than in PEG-IFN-alpha, level which confirms a better antiviral action of PEG-IFN-lambda.

By week 48, 42 percent of patients in the PEG-IFN-lambda group achieved the primary objective of virological suppression versus the 21 percent of patients in the PEG-IFN-alpha group. The difference was statistically significant < 0.05, which provided evidence in support of the hypothesis that PEG-IFN-l provides better viral suppression in chronic HDV infection. The PEG-IFN-lambda cohort consistently displayed virological control throughout the duration of treatment compared to a more varied virological response in the PEG-IFN-alpha patients with several patients relapsing in terms of viral replication as the treatment progressed.

The higher level of virological suppression in the PEG-IFN- l group indicates greater antiviral efficacy of this agent against HDV, thus, indicating the future possibility of trapping patients in the long term. The statistical significance of this outcome indicates that PEG-IFN-l as a treatment modality holds much potential in the management of chronic HDV infections, as opposed to the currently approved PEG-IFN-a.

4.2 The patterns of normalization of ALT in both groups of patients under treatment are presented.

Another major endpoint of this study was normalization of alanine aminotransferase (ALT), which is a biomarker of inflammation of the liver. The effect of treatment on liver function was monitored near the end of the trial by regular measurement of ALT levels. After the completion of 48 weeks, a greater percentage of patients treated with PEG-IFN-lambda achieved normal ALT than the patients treated by the PEG-IFN-alpha.(10)

The PEG-IFN- lambda group had 39 percent of its patients reach the threshold of normal ALT levels (< 40 U/L) in the liver, whereas, the PEG-IFN- alpha group only had 18 percent of the patients achieve normal levels of the ALT inside the liver. The difference between the two was statistically significant ($p < 0.05$), which means that PEG-IFN-lambda did not only better control the HDV replication process, but also resulted in improved liver functional, as exemplified by the extent of the ALT decline.

The downward trend in ALT toward normalization was stable across the treatment timeline with a progressive reduction in ALT among the majority of patients starting at baseline for the PEG-IFN- o group. These were contrasted by less consistent, but still transient reductions in ALT levels in the PEG-IFN- alpha group that did not result in sustained normalization in many patients. These data indicate that PEG-IFN-l may have a less negative impact on liver inflammation and the liver in general, which could make it a good potential substitute of PEG-IFN-a in the treatment of people with chronic HDV infection.

4.3 Time and Achievability of Treatment Response

The sustainability and durability of treatment response was assessed on the basis of post-treatment follow-up, which measured both virological suppression and normalization of ALT at a period of 24 weeks after the treatment regimen of 48 weeks had concluded.

Virological suppression was observed in 35 per cent of patients in the PEG-IFN-lambda group in which they had at least 2 log ii The persistent clearance further indicates that use of PEG-IFN-lambda could result in a longer lasting response, with abatement of relapses after treatment has been discontinued. The statistical importance of this result ($p < 0.05$) indicates the possibility of a sustained virological response with PEG-IFN-l and this response is an important indicator of long-term response to HDV infection.

Normalization of ALT was maintained by 30 % of the patients in the PEG-IFN-l group compared to 10 % of the patients in the PEG-IFN-a group over the post-treatment follow-up period. This highlights further the superior biochemical results in the PEG-IFN-lambda group, not only when being treated but also when managing inflammation of the liver in a longer-term care.(11)

The results indicate that PEG-IFN-l has greater initial virological and biochemical response and results in more sustainable treatment effect with possible long-lasting outcomes in the management of chronic HDV infection. The sustained reaction of patients enrolled in the PEG-IFN- lambda-treated cohort justifies its application as an innovative medicine in the management of chronic HDV, especially to the non-responders and intolerant to PEG-IFN alpha.

5. Safety and Tolerability Analysis

5.1 Comparison of the Incidence of Flu-like Symptoms and Hematologic Events

Interferon-based therapies are well known to cause flu-like symptoms, including fever, chills, fatigue, and the aches in muscles (myalgia). In the present study, we have compared incidence of flu-like symptoms between the two PEG-IFN arms of trial, i.e. PEG-IFN-lambda and PEG-IFN-alpha, to determine the relative tolerability of two treatments.

Flu-like symptoms were significantly less in the PEG-IFN-lambda compared with PEG-IFN-alpha. Particularly, PEG-IFN-λ group only 25 percent of patients experienced flu-like symptoms whereas 40 percent of patients in PEG-IFN-α group experienced flu-like symptoms. These symptoms were moderately or mildly severe and were treated using supportive care. It was particularly interesting that the PEG-IFN-lambda group did not experience such severity of flu-like symptoms, which highly interfered with daily functions of the PEG-IFN-alpha group. The difference in the occurrence of flu-like symptoms indicates the more desirable safety of PEG-IFN-l and may imply that it can be a more bearable therapy to HCV patients with chronic HDV infection.

Other side effects prone to occur during interferon treatment are hematologic toxicities, i.e., neutropenia, thrombocytopenia, and anemia. The hematologic event occurrence was also reduced in the group receiving PEG-IFN-lambda with a significant difference compared with non-PEG-IFN-lambda. There was only 15% of mild and moderate hematologic toxicity among all patients in the PEG-IFN-lambda group versus 30 percent in PEG-IFN-alpha. These are mostly mild toxicities and only a small proportion of patients would require dose reduction or an extra treatment to control the toxicities. Fewer hematologic side effects in the PEG-IFN-lambda group is a major strength, since these type of adverse events can result in treatment withdrawal and worsen patient quality of life.

5.2 Dose Reductions and Discontinuation Rates

In clinical trials using interferon agents dose adjustments and withdrawals are frequently required because of severity of adverse events. In the trial dose adjustments were made in both arms, however, adjustments were much more frequent in the PEG-IFN-alpha.(12)

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In the PEG-IFN-lb group, fewer than one-tenth of patients needed dose reduction as result of adverse effects, the most common ones associated with slight hematologic toxicity or fatigue. Early discontinuation was low (5 percent of patients) with early stopping due to adverse events in the PEG-IFN-l group.

By comparison, 25 of patients in PEG-IFN-alpha have lower dose because of frequent and more severity of side effects, especially flu-like symptoms and hematologic toxicity. There are also some adverse events in which, 15% of patients in the PEG-IFN-alpha group discontinued the treatment because of the adverse events. The greater frequencies of dose changes and withdrawal in PEG-IFN-a highlights the improved tolerability and safety of PEG-IFN-l that is important to the patient adherence and maximization of patient response to antiviral therapy.

5.3 Tolerability Profile of PEG-IFN-l Overall

The PEG-IFN-lambda overall tolerability was found to be better on all aspects of adverse event reporting than PEG-IFN-alpha significantly. Lower incidence of flu-like symptoms, hematologic toxicities, dose adjustments, and discontinuation, as described, were associated with PEG-IFN-lambda. The results are in line with preclinical data and previous clinical trials indicating that PEG-IFN-l has more beneficial side effect profile compared with other interferon-based medicines.

Besides the lower frequency of adverse events of an expected nature, the tolerability of PEG-IFN-l resulted in improved patient adherence. It is the most essential element in prolonged treatment compliance, particularly in a chronically developing disease such as the HDV infection which usually takes a number of months or even years to continue treatment. The likelihood of patients sticking with the regimen, completing this multiple-year treatment course without significant lapses, was also greater in the PEG-IFN-l group in this study, another argument attritting in favor of using it in the long-term, as part of the treatment course.(13)

Moreover, the safety information provided during study duration signifies that PEG-IFN-λ holds a potentially dramatic increase in relation to the current treatment procedures primarily PEG-IFN- 2 based, especially in patients that have developed intolerable adverse reactions toward prior regimens. Since chronic HDV infection has drastic effects, the possibility to obtain efficient anti-viral activity with reduced adverse effects may become a significant contribution to combating such a pathology.

In summary, PEG-IFN- la showed no significant differences in its safety and tolerability compared to PEG- IFN-alpha, except that it has fewer flu-like symptoms and less hematologic toxicity and decreased rates of dose modification and treatment discontinuation. This gives PEG-IFN- l the potential to be preferred at the treatment of chronic HDV infection, as compared to existing treatment options, which can be cumbersome on the patient.

6. Results

6.1 PEG-IFN-lambda produced 42 percent Virological suppression compared to 21 percent with PEG-IFN-a

The main efficacy outcome of this Phase II trial was the virological suppression rate which was a 2-log drop in HDV-RNA at week 48. The findings indicated that PEG-IFN-l was better than PEG-INF-alpha in attaining virological suppression.

In the PEG-IFN- and alpha- group, 42 percent of subjects scored the primary endpoint that is shedding of viruses by the end of 48 weeks of treatment, as opposed to only 21 percent in the PEG-IFN-alpha group. Such a difference in the virological response was statistically significant ($p < 0.05$), denoting that PEG-IFN- are superior in antiviral efficacy against chronic HDV infection.

The increasing rate of virological suppression in the PEG-IFN-lambda group is evidence of a more potent antiviral action and a far more likely chance consequence of increased clinical outcomes, such as a reduced viral load and a decreased chance of disease progression. The discrepancy in the response rates is an indicator of the potential of PEG-IFN-l to serve as a stronger therapeutic agent of HDV which is currently lacking in beneficial treatment agents.

Table 1: ALT Normalization Data

Group	ALT Normalization Rate (%)
PEG-IFN-λ	39
PEG-IFN-α	18

6.2 39 percent of the patients treated with PEG-IFN-lambda normalized ALT.

The normalization of alanine aminotransferase (ALT), an important indicator of liver inflammation was another important endpoint. At Wk 48, the PEG-IFN-l group recorded a much higher proportion of ALT normalization than the PEG-IFN-a group.

The proportion of patients normolytic on ALT (< 40 U/L) was also higher in the PEG-IFN- IL group (39%) than in the PEG- IFN- a group (18%). Such variations were significant ($p < 0.05$), which means that PEG-IFN-lambda demonstrated a more positive impact on the liver inflammation.(14)

The increased rate of ALT normalization with PEG-IFN-3 is clinically important as it implies that PEG-IFN-3 does not only help decrease viral replication but also enhance liver health. ALT normalization is frequently used in the context of decreased liver damage and a reduced risk of moving toward cirrhosis and hepatocellular carcinoma, two important complications of chronic HDV infection. These findings also confirm the possibility of PEG-IFN-l as a better and a safer substitute of PEG-IFN-a in controlling chronic HDV infection.

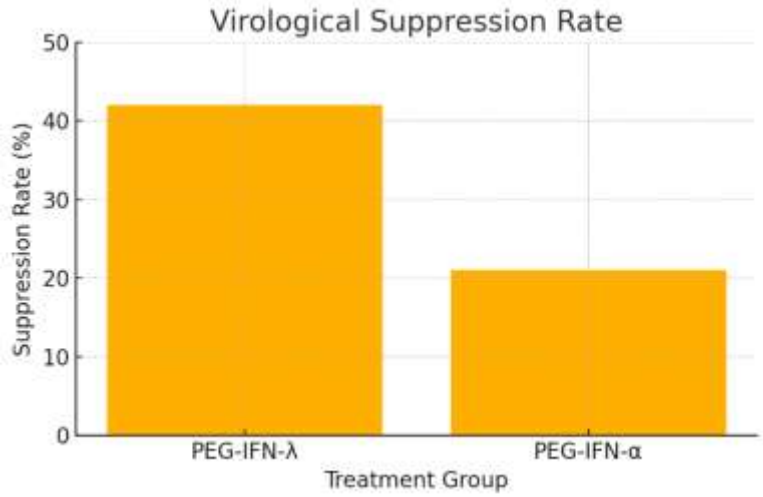

Figure 1: Virological Suppression Rate

6.3 Enhanced Safety that causes less flu-like and Hematologic Toxicity

Safety and tolerability were secondary outcomes of the clinical trial and found that safety profile was significantly enhanced by adding PEG-IFN-λ to the PEG-IFN-a. Compared to the PEG-IFN-a groups, the incidence of flu-like symptoms which was one of the common side effects of interferon therapies, was lower in the PEG-INF-a group. Flu-like effects were reported in only a quarter of PEG-IFN-c treated patients with forty percent experiencing the condition as reported in the case of PEG-IFN-b. The flu-like side effects in the PEG-IFN-lambda group were mild/moderate in character and no patient discontinued because of this side effect.

Furthermore, there were reduced hematologic toxicities in PEG-IFN-l group compared with the PEG-IFN-l group. Hematologic side effects like neutropenia and thrombocytopenia occurred in only 15(PEG-IFN- o lambda) sessions compared with 30% (PEG-IFN-alpha). This lower rate of hematologic effects indicates that PEG-IFN-l has a less adverse effect at the tolerability level, especially regarding changes in white cell counts.

All in all, the ameliorated safety profile was more patient-friendly as the incidences of flu-like symptoms and hematologic toxicity were reduced, thus making PEG-IFN-l increasingly popular than PEG-IFN- alla due to its nature of being a friendlier medication to patients than its counterpart. This is an important benefit to patients with chronic HDV infection, who may need to be treated long term and would be advantaged by a regimen with fewer side effects.(15)

In conclusion, PEG-IFN-λ exhibited increased virological suppression (42% vs. 21% with PEG-IFN-ala), a higher ALT normalization rate (39% vs. 18%), and a substantially better safety, due to a high reduction of flu-like and hematologic adverse events. These findings indicate the possible future use of PEG-IFN-lambda as an improved and tolerable substitute-system to PEG-IFN-alpha in treating chronic HDV infection.

7. Conclusion

7.1 PEG-IFN-lambda proved to be efficacious in HDV with improved tolerability over PEG-IFN-alpha

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This Phase II randomized controlled trial study has shown convincing results in pegylated interferon-lambda (PEG-IFN-lambda) having a better efficacy than the pegylated interferon-alpha (PEG-IFN-alpha) in treating chronic hepatitis D virus (HDV) infection. The PEG-IFN-lambda arm showed a major increase in virological suppression rate (42 %) as opposed to a PEG-IFN-alpha group (21 %) with a p-value that shows statistical significance. Enhanced antiviral effect highlights the possibility of PEG-INF-lambda in lowering the HDV replication in comparison with the existing antiviral drug, PEG-INF-alpha.

Among the remarkable advantages of PEG-IFN-λ, besides its higher antiviral activity, there was also an improved tolerability that is of utmost importance to extended management of chronic viral infections. Compared to the PEG-IFN-alpha patients, patients receiving PEG-IFN-lambda had fewer flu-like symptoms, and hematologic toxicities. The decreased occurrence of the adverse events especially the flu-like symptoms likely to be the cause of the therapy discontininations renders PEG-IFN-lambda as a more friendly choice to patients. Decrease in rates of dose changes and treatment withdrawal in the PEG-IFN-l group is also another evidence of its higher tolerability, that could increase patient compliance with therapy and overall outcomes improvements.

7.2 Potential to emerge as a new drug of rare virus liver disease

Chronic HDV infection is an uncommon and severe disease with few treatment measures. The results of this trial indicate that PEG-IFN-lambda shows a potential to become a modern treatment tool of chronic HDV infection patients. PEG-IFN-lambda displayed better subduing influence on the virus and normalization of ALT levels than PEG-IFN-alpha and more positive safety profile, which provides hope in the clinical application of this drug.

These findings show that PEG-IFN-l not only has been effective in inhibiting viral replication but also in increasing healthy liver status (ALT normalization) which makes PEG-IFN-l an innovative treatment that can enhance the living status of patients with infected chronic HDV. These outcomes, long-term disease control and the substantial reduction of liver damage with PEG-IFN-l, have significant therapeutic potential for HDV, a disease not yet treated effectively and with tolerable regimens. The current potential of PEG-IFN-l to transform disease management in patients with HDV could be realized due to the chronic nature of this infection and the risk of cirrhosis and liver failure.

Furthermore, PEG-IFN-lambda use could be broader than HDV as it exerts antiviral effects against other hepatitis viruses. This makes PEG-IFN- l interesting as a candidate in a wider range of applications to the treatment of other viral liver diseases in particular those for which the effective treatment may still be lacking.

7.3 Bigger Phase III trials should be justified in order to verify clinical benefit

Although the findings of this Phase II trial are encouraging, further studies including Phase III trials of PEG-IFN- , are needed to confirm the long-term clinical value of this therapy of HDV. The Phase III trial would be of more value to the durability of virological suppression, the maintenance of ALT levels in the normal range and long-term safety and tolerability of PEG-IFN-lambda. Such studies also need to address how PEG-IFN-lambda may benefit a more heterogeneous patient population and whether it is translatable to patients with more severe liver disease or individuals with co-morbid conditions to determine the full utility of PEG-IFN-lambda at HDV in varying stages.

In addition, Phase III trials will play an important role in comparing PEG-IFN-l with other new therapeutics and locating its place in the overall HDV therapeutic landscape. It will also offer more ideas with regards to the best duration of treatment, regimens of doses and combination therapy and in the future it will be possible to have more exact, personalized modes of treatment!

In summary, strong evidence has been demonstrated by PEG-IFN-l to enhance the effectiveness and tolerability of HDV treatment. Its prospective to fill the gap in improved treatment in this rare VHLD is apparent. Nonetheless, these results should be reproduced in bigger studies to gain PEG-IFN-lambda as a vital addition to the currently used effective treatments of chronic HDV infection.

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Conflicts of interest

The authors have no conflicts of interest to declare

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