EDITORIAL

DOI: http://dx.doi.org/10.15403/jgld-5627

A New Dawn in Hepatitis D Management

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Received: 04.04.2024
Accepted: 19.04.2024

The battle against hepatitis D (HDV) infection, the most severe form of viral hepatitis, has long been fraught with challenges. This disease, known for its rapid progression to cirrhosis and liver cancer [1, 2], poses a significant burden worldwide, affecting 12 to 72 million people [3-5]. Globally, HDV infection remains a critical public health issue, with varying prevalence rates across different regions. It continues to be overlooked, underestimated, and insufficiently treated. In Romania, the high prevalence of HDV [6, 7] has underscored the urgent need for effective therapeutic strategies and has catalysed remarkable research efforts within the country.

All chronic hepatitis D (CHD) patients are potential candidates for antiviral therapy. Of course, all patients with active liver disease, advanced liver fibrosis or compensated cirrhosis should be treated, as a successful treatment may result in improved clinical long-term outcomes [8, 9], but there are no treatments yet available for patients with more advanced liver disease such as CHD-related decompensated cirrhosis. Liver transplantation is their only option.

Until recently, the standard of care for the antiviral therapy of delta hepatitis was the use of pegylated interferon alfa (PegIFNα), based on data from the HIDIT-I and HIDIT-II trials [10, 11]. Despite the fact that it has never been approved for this indication, it has been widely used off-label for almost two decades, as the only therapeutic option for treating patients with delta hepatitis in real world scenarios. The efficacy has been rather limited, with response rates of 17 to 29% and a relapse rate higher than 50% in those who respond to therapy [12, 13]. Several attempts to increase the response rate by adding oral nucleos(t)ide analogues used against the hepatitis B virus (HBV) such as tenofovir or adefovir or prolonging the duration of therapy to 96 weeks, did not yield any significant improvement in the virological response. Moreover, advanced liver disease and side effects limited the access to PegIFN-based therapy. Our own experience indicated virological responses in 24-25% of CHD patients treated with PegIFN and biochemical responses in 50-56% of these patients. However, a combined biochemical and virological response was observed in only 16.7% of patients after 104 weeks of follow-up [14, 15]. It is noteworthy that over 50% of the patients exhibited significant liver fibrosis at the initiation of therapy. During follow-up, these patients experienced a significant decrease in the necroinflammatory score, assessed by the Knodell score, and a tendency towards decreased fibrosis score, although this did not reach a statistically significant level.

The introduction of new antivirals, such as Bulevirtide (BLV), Lonafarnib (LNF), nucleic acid polymers (NAP) or PegIFN lambda, has marked a significant milestone, offering hope and new treatment avenues [16]. On July 2023, BLV 2 mg per day in subcutaneous administration received unconditional marketing authorization by the European Medical Agency (EMA) as specific therapy for chronic HDV infection, with the recommendation to maintain the treatment until clinical benefit (either virological, biochemical, histological, or noninvasive evaluation of liver stiffness) is observed [17]. After one year of therapy, 12% of patients receiving BLV 2 mg per day achieved undetectable HDV RNA levels, and 45% showed a combined (virologic and biochemical) response, defined as undetectable/more than 2log decrease of viral load and aminotransferases normalisation. Given that, the ideal duration for BLV therapy in order to secure a lasting virological response remains undetermined, prolonging BLV treatment to more than one year being presently considered the most effective approach to enhance or sustain the virological response [18, 19]. The use of PegIFN in combination with BLV markedly enhanced the short-term clearance of HDV RNA, demonstrating a significant synergistic impact. A recent

meta-analysis [20] demonstrated that a combination of IFN and BLV holds the greatest promise as a therapeutic strategy to potentially improve long-term outcomes or achieve a cure for CHD.

In this issue of JGLD, we regret to inform you that the study titled ‚Results of Response-Guided Therapy with Pegylated Interferon Alpha 2a in Chronic Hepatitis B and D' by Gherlan et al. [21] has been withdrawn from our journal. The study was simultaneously submitted to another journal without our prior knowledge. It should be noted that this article [21] does not provide any new insights into the field of HDV hepatitis. A prior study [22] already indicated that measuring HDV RNA levels at the 24th week of PegIFN therapy, either alone or combined with adefovir for a duration of 48 weeks, can predict which patients will have a negative HDV RNA test result 24 weeks following treatment completion. Additionally, a reduction in HDV RNA levels exceeding 2log at week 24 of therapy was effective in identifying null responders, with a negative predictive value of 95%. The virological response obtained in Gherlan's study are similar to all reported rates in other previously published studies in literature. Furthermore, the study's findings are not a valuable addition to the current understanding and management of HDV, emphasizing the continued need for novel therapies to improve patient outcomes [21]. Moreover, the necessity of stopping rules in HDV therapy with PegIFN is questionable. Given the variable response rates and the complexity of HDV infection, rigid stopping rules may not be beneficial. These rules can prematurely halt treatment for patients who might eventually respond with a longer duration of therapy. Instead, a more flexible and individualized approach could be more effective, allowing clinicians to adjust treatment based on a comprehensive assessment of the patient's progress and overall health status. This strategy avoids the potential drawbacks of a one-size-fits-all stopping rule and supports a more nuanced management of HDV, where continuous monitoring and adaptation of therapy can better address the needs of each patient. The integration of novel antivirals, coupled with refined treatment protocols informed by rigorous research, sets the stage for significant advancements in HDV treatment. Personalization and predictors of response and timing for stopping therapy while maintaining efficacy are even more crucial in the context of new anti-HDV antivirals, and this should be explored. These developments showcase the continuous drive for innovation in battling HDV, underscoring the necessity of modifying and advancing treatment approaches to effectively tackle this challenging virusAgents like BLV, LNF or nucleic acid polymers remain out of reach for most resource limited areas where access to new therapies are significantly delayed by years to decades. Strategies to facilitate access to care for the most vulnerable should be actively sought by all stakeholders.

The objectives for eliminating viral hepatitis are challenging and receiving growing focus. The Global Health Sector Strategy on Viral Hepatitis for 2015–2021 did not explicitly consider hepatitis D [23]. Addressing the deficiencies in hepatitis D management is essential for meeting the global targets of eradicating viral hepatitis by 2030.

Conflicts of interest: None to declare.

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