ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Update on Treatment for Hepatitis Delta

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G&H Before the recent drug approval for hepatitis delta, how was this disease treated?

TK Prior to the approval of bulevirtide (Hepcludex, Gilead) by the US Food and Drug Administration (FDA) on May 22, 2026, treatment for hepatitis delta was very limited. As a result, many patients with hepatitis delta were left untreated. There were (and continue to be) significant gaps in care and very low rates of testing for hepatitis delta and linkage to care; many providers figured that there was not much to do because of the limited treatment options. The only available treatment was pegylated interferon, and despite it being off-label for hepatitis delta, guidelines from the American Association for the Study of Liver Diseases recommended that patients with hepatitis delta could be treated with pegylated interferon for 1 year. The recommendation was fairly broad in that pegylated interferon therapy could be used for patients with elevated hepatitis delta virus (HDV) RNA and alanine aminotransferase (ALT) levels, which most patients with hepatitis delta have. However, despite this recommendation, pegylated interferon was used relatively infrequently because not only did it have somewhat limited efficacy, but it was also associated with a range of adverse effects, including flu-like symptoms, fatigue, cytopenias, and neuropsychiatric symptoms, which limited its tolerability and treatment adherence. As a result, there was a lot of hesitancy, understandably, on the part of providers and patients to initiate treatment with pegylated interferon and stay on it for a year.

> For the first time, there is a drug that is FDA-approved for the treatment of hepatitis delta.

G&H What data led to the approval of bulevirtide, and how does it change first-line management of this disease?

TK The data came from MYR 301, a study published in *The New England Journal of Medicine* in 2023 that evaluated the efficacy of bulevirtide 2 mg or 10 mg, compared with a delayed treatment arm or placebo, for 48 weeks. The primary endpoint was the FDA-prespecified endpoint of a reduction in HDV RNA by at least 2 $\log_{10}$ IU/mL and ALT normalization. The investigators found that 45% of patients in the 2-mg group and 48% in the 10-mg group, compared with only 2% in the delayed treatment arm, were able to achieve this primary endpoint response.

The approval of bulevirtide changes the treatment possibilities for patients with hepatitis delta significantly. As I mentioned, pegylated interferon was not commonly used and not tolerated by many patients, whereas bulevirtide is much better tolerated and effective. For the first time, there is a drug that is FDA-approved for the treatment of hepatitis delta.

G&H Is this agent appropriate for all patients with hepatitis delta?

TK Bulevirtide is administered via a daily injection, so patients who opt for this treatment have to be able to adhere to an injection every day. Preparation involves patients reconstituting the medication themselves, so they need to be capable of following medication preparation instructions. Nevertheless, bulevirtide can be used by

many patients with hepatitis delta; there is no minimum fibrosis requirement for drug initiation and there are no significant medication interactions. The only subgroups for whom bulevirtide is not approved are patients with decompensated cirrhosis and patients with hepatitis delta post–liver transplant.

It should be noted that, although the 2-mg dose is approved in Europe, the 10-mg dose is approved in the United States. However, the packaging of bulevirtide in the United States reads 8.5 mg because that is the amount of the drug directly delivered to the patient. This is not a new, unstudied dose; it is, in fact, the 10-mg dose evaluated in studies.

G&H Does pegylated interferon still have a role in hepatitis delta treatment?

TK This is an active area of discussion in the hepatitis delta scientific community. There is still interest in the potential combination therapy of bulevirtide and pegylated interferon. The phase 2b MYR 204 study, published in 2024 in *The New England Journal of Medicine,* evaluated combination therapy with pegylated interferon plus bulevirtide, compared with bulevirtide alone. The MYR 204 study evaluated outcomes of hepatitis delta after a finite treatment duration. The primary endpoint was to achieve an undetectable hepatitis delta level at 24 weeks after completing treatment. Patients who received combination treatment with pegylated interferon and bulevirtide had significantly higher rates of reaching the primary endpoint compared with those receiving bulevirtide alone. In fact, 46% of the patients in the 10-mg bulevirtide and pegylated interferon arm and 32% in the 2-mg bulevirtide plus pegylated interferon arm reached the endpoint, compared with only 12% in the bulevirtide-only arm. Thus, there is ongoing discussion about whether combination treatments can be offered with the goal of having a more finite treatment duration that would lead to higher rates of undetectable HDV RNA after treatment completion. Given these study results, there may still be a role for pegylated interferon, and, in fact, in certain parts of Europe, many providers are prescribing both medications together.

G&H How should patients be counseled about treatment duration?

TK At the moment, when bulevirtide is prescribed, patients should be counseled that this treatment is intended for long-term use. There are no clear stopping rules; the package label says to continue treatment as long as it is associated with a response. Patients should not just stop on their own; they should continue treatment because there may potentially be worsening of liver disease if treatment is stopped. Data have recently been published from longer-term follow-up evaluating patients after the end of treatment. The investigators looked at patients who were treated for 144 weeks in the MYR 301 study and then followed them to 240 weeks (96 weeks after they stopped treatment). One of the main study findings is that the longer the patient has undetectable HDV RNA on treatment, the more likely they are to have a sustained undetectable viral load after stopping treatment. Although this was a small study, among patients on treatment who maintained an undetectable viral load for 96 weeks, 90% had a sustained undetectable viral load off treatment once they stopped. In contrast, patients who had an undetectable viral load for less than 48 weeks while on treatment and then stopped had less than a 10% chance of having an undetectable viral load off treatment. This type of data may eventually help to inform which patients are able to stop treatment, but patients should not be stopping on their own. Counseling should be done upfront so patients expect to stay on treatment long term and do not stop without speaking with their provider.

There are several promising medications that are being actively evaluated, including in phase 3 studies.

G&H How should patients be monitored?

TK I recommend monitoring patients a little more closely when starting treatment. I would probably see patients monthly during the first 3 months to make sure they are tolerating the medication and that there are no side effects. Afterward, I would space monitoring out to every 3 months, and maybe even potentially every 6 months, if patients are doing well without any side effects and do not have advanced liver disease. Relatively frequent check-ins are important, especially in the beginning, because clinical trial data as well as real-world data show that adverse effects such as injection site reactions do occur.

G&H What are the most promising drugs in the hepatitis delta pipeline?

TK This is a very exciting time for hepatitis delta. There are several promising medications that are being actively

evaluated, including in phase 3 studies. One of the agents in development is the monoclonal antibody brelovitug (Mirum), which is being evaluated with weekly or monthly injection doses. Early phase 2b data presented at this year's meeting of the European Association for the Study of the Liver showed that the drug was effective and safe and that the primary endpoint was being met. Also promising is a combination regimen of a silencing RNA agent (elebsiran) and monoclonal antibody (tobevibart) from Vir. This monthly injection combination was shown to be effective and safe in a phase 2 study and was tolerated well overall, and it is actively being investigated in the phase 3 study program ECLIPSE. Another monoclonal antibody, libevitug (Huahui Health), is also being studied in phase 3 research for hepatitis delta. Lastly, lonafarnib (EIT Pharma) should also be mentioned. This agent is being reevaluated in a phase 3 program in combination with pegylated interferon and without. A significant benefit is that lonafarnib is an oral agent, not an injection. However, it is associated with fairly significant gastrointestinal side effects, somewhat limiting enthusiasm.

G&H How do you see these agents potentially fitting alongside or replacing bulevirtide monotherapy?

TK Ultimately, it is good to have multiple treatment options for our patients, and there will be different factors that will hopefully drive shared decision-making in terms of which of these agents to use. Currently, only bulevirtide is approved, so decisions would involve whether to utilize bulevirtide as a monotherapy or consider combination with pegylated interferon. Additionally, if there is access to clinical trials, providers should discuss with patients whether they would potentially benefit from participation in an ongoing clinical trial for hepatitis delta vs starting on bulevirtide. A few of the agents that I mentioned are currently undergoing studies directly comparing efficacy and safety between them and bulevirtide. Those results will help inform our discussions. Aside from efficacy, doctors will need to speak with patients about preferences in terms of doing daily vs weekly injections and having them done in clinical practice vs at home. Such practical considerations will come into play.

Another aspect that will be relevant is that bulevirtide has been around for some time now. It has been approved in Europe for years, so there has been an accumulation of a significant amount of real-world data. Seeing that bulevirtide has already been used by many may be an aspect that is important to patients; it may comfort them that more is potentially known about this agent than about the newer ones.

G&H What further research is needed in this area?

TK The most exciting research in hepatitis delta involves the new therapies that are being evaluated. Aside from treatment, there is a lot of discussion in the field about how to best identify patients with hepatitis delta, optimize linkage to care, and improve diagnostic and monitoring tools for hepatitis delta. There is ongoing research on hepatitis delta testing in order to optimize HDV assay sensitivity and specificity. Additionally, there is a need to increase provider awareness of hepatitis delta so that appropriate hepatitis delta testing is performed. Reflex testing programs should be implemented so that every person with hepatitis B is automatically screened for hepatitis delta to avoid missing any infected patients and to make sure they are linked early to treatment. In addition, more research is needed into the natural history of hepatitis delta to try to understand the key predictors of disease progression, which patient subgroups are at highest risk and thus need to be treated early, and which patients may have a more indolent course of hepatitis delta.

Disclosures

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Suggested Reading

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