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Treating chronic hepatitis delta: The need for surrogate markers of treatment efficacy

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Summary

Chronic hepatitis delta represents the most severe form of chronic viral hepatitis. The current treatment of hepatitis delta virus (HDV) infection consists of the use of interferons and is largely unsatisfactory. Several new compounds are currently in development for the treatment of HDV infection. However, surrogate markers that can be used to develop clinical endpoints in HDV infection are not well defined. In the current manuscript, we aimed to evaluate the existing data on treatment of HDV infection and to suggest treatment goals (possible "trial endpoints") that could be used across different clinical trials.

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Introduction

Chronic hepatitis delta (CHD) has been designated an orphan disease in the European Union and in the US.[1] In these areas CHD is observed mainly in high-risk groups such as intravenous drug users, sex workers and immigrants from hepatitis delta virus (HDV) endemic areas. The latter represent areas and countries such as the former Soviet republics, Western Pacific islands, Mongolia, Pakistan, Afghanistan, countries of sub-Saharan Africa, Mediterranean and Eastern European countries such as Turkey, Romania and Albania, and areas close to the Amazon river in South America.[2] The causative agent of CHD, HDV, contains the smallest genome of any animal virus and needs the helper function of the hepatitis B virus (HBV) to propagate and to cause disease in humans.[3–6] Eight genotypes of HDV have been described based on 19–38% sequence variation.[7,8] Determination of HDV genotype and the global distribution of these genotypes may be important as they may affect disease prognosis and treatment outcome. For example, HDV genotype 2 appears to have a milder course than genotype 1,[9] and genotype 3 has been associated with a more severe form of the disease.[10] Furthermore, genotype 5 may be associated with outcomes similar to genotype 2, with a milder form of disease and may also respond better to interferon alpha (IFNα).[11] Interestingly, genotype 3 may also respond better to IFNα.[12] Among these genotypes, genotype 1 has a worldwide distribution whereas genotypes 2 and 4 are seen mainly in the Far East, genotype 3 in northern South America and genotypes 5 to 8 have only been seen in Africa.

CHD represents the most severe form of chronic viral hepatitis. Not surprisingly, many patients with compensated liver disease entering clinical studies in CHD have already reached the stage of cirrhosis. In studies from HIV-HDV coinfected patients, HDV was found to be independently associated with an increase in mortality.[13,14] This may justify a more aggressive treatment approach with a rebalanced risk/benefit ratio compared to HBV or HCV monoinfection. Despite this, treatment of CHD has not changed since the 1980s and consists of the off-label use of IFNα or pegylated (peg)-IFNα with a viral response observed in only 25 to 30% of genotype 1 patients.[15] However, considering the possibility of late relapse after discontinuation of IFN treatment, as will be discussed, the true viral response rate to IFN is almost certainly even lower. The low response rate is not unexpected. Studies in transfected cell lines suggested a general insensitivity of HDV RNA replication to IFNα.[16,17] Interferons may be effective at a very early stage of infection when HDV is entering hepatocytes rather than at the stage of established intracellular hepatocyte HDV infection.[17,18] Human pharmacokinetic studies were supportive of these *in vitro* studies and a much longer delay was observed before PegIFNα had an effect on HDV RNA compared to HCV RNA or HBV DNA (8.5 days *vs.* 10 to 20 hours, respectively).[19] At present, there is no approved therapy for CHD and without new treatment options many patients will die from liver disease, with liver transplantation providing the only hope of rescue.

However, after many years of silence there are now attempts to develop new treatments in CHD. Four approaches have raised most of the attention, with the efficacy and safety of drugs linked to these approaches currently being tested in phase II trials. These compounds include an HBV-specific entry inhibitor, a prenylation inhibitor, nucleic acid polymers and interferon lambda (IFNλ).[20–23] In addition, there are several new treatments aimed at inducing functional cure of HBV, which could also be beneficial for HDV if HBV surface antigen (HBsAg) seroconversion is achieved. These include immunomodulatory approaches such as the use of Toll-like receptor ligands, therapeutic HBV vaccines and check point inhibitors, as well as novel antivirals such as the use of small interfering RNAs, capsid assembly modulators and gene editing approaches.[24]

The aim of all forms of treatment in chronic viral hepatitis is to prevent the development of complications of liver disease such as hepatocellular carcinoma, cirrhosis and decompensation, and ultimately death. Surrogate markers of treatment efficacy are used if the overall aim of treatment can be achieved. These surrogates have been well defined for both chronic hepatitis B and chronic hepatitis C[25,26] but not for CHD. The main objective of this report is an attempt by a group of experts in the field to come up with reasonable and realistic recommendations with regard to treatment goals, which could be used as trial endpoints that will represent a clinically meaningful basis for conditional approval of new drugs in CHD – a disease that may not be curable and in which long-term placebo controlled studies with hard endpoints are not feasible.

Endpoints and predictors of response used in clinical trials to date for CHD

Importance of HDV RNA measurements

In recent years, many clinical trials have studied the effects of PegIFNα, nucleos(t)ide analogues and their combination. In the HIDIT-1 study which included 91 patients and was at that time the largest study ever performed in CHD, the primary endpoint was the achievement of undetectable levels of HDV RNA and normal levels of alanine aminotransferase (ALT) at end of treatment.[27] Similarly, in the HIDIT-2 Study, end of treatment HDV RNA negativity was the primary endpoint.[28] As secondary endpoints in these 2 studies and as primary endpoints in many other studies, undetectable HDV RNA at week 24 post-treatment was explored, with the expectation that it might be associated with sustained virologic response. However, a 5-year follow-up of the HIDIT-1 study revealed that more than 50% of patients with undetectable HDV RNA at 6 months post-treatment developed detectable HDV RNA at least once during follow-up.[29] All (7 out of 7, 100%) patients with long-term virologic response were reported to have displayed reduced biochemical disease activity (low ALT) whereas only 4 out of 9 (44%) patients with late relapse did so.

Sequencing of pre- and post-treatment serum confirmed that viral relapse had occurred, suggesting that some form of HDV latency exists in patients where HDV RNA was transiently undetectable in blood. High infectivity of HDV was suggested as the likely cause of the lack of durability of the viral response,[30] based on observations in early chimpanzee studies where infectious serum diluted as much as 10^{11} times was still able to transmit HDV to HBsAg-positive chimpanzees.[31] Further, one may add the limitation of HDV RNA testing by PCR, as the assays used may not be sensitive enough.[32] Thus, it does not seem to be appropriate to use the term sustained virologic response for HDV, in the same manner as in hepatitis C.

The role of HDV RNA measurements to predict the achievement of undetectable HDV RNA has also been explored. HDV RNA levels at on-treatment week 24 were the most studied. HDV RNA negativity at week 24 was associated with undetectable HDV RNA at post-treatment week 24, both for conventional IFNα as well as PegIFNα treatment.[33,34] A sub-analysis of the HIDIT-2 study revealed that earlier on-treatment time points, *e.g.* HDV RNA kinetics at treatment weeks 4, 8 or 12, were less predictive.[35]

Quantitative HBsAg assessment

Quantitative HBsAg levels have been assessed in several studies for their potential to predict whether a patient will achieve HDV RNA undetectability. In a sub-analysis of the HIDIT-1 study, any decrease of quantitative HBsAg levels at on-treatment week 24 was more often observed in patients who had undetectable HDV RNA at end of treatment (week 48). On-treatment week 24 HBsAg levels were also lower in patients with undetectable HDV RNA at post-treatment week 24.[33] However, HBsAg measurements (either absolute levels at end of treatment or decline from baseline) were not independent predictors of response. A more definite role for quantitative HBsAg levels has been defined in a recent study from Italy.[36] All patients who cleared HBsAg after PegIFNα treatment had on-treatment week 24 HBsAg levels less than 1,000 IU/ml. These findings are also in line with a previous case series of patients treated at the National Institutes of Health (NIH) where an HBsAg decline after 12 weeks was associated with long-term virologic response in patients treated for up to 5 years with PegIFNα.[37]

As the ideal endpoint, HBsAg clearance, is rarely achieved in CHD, there is a need to define whether patients not achieving an HBsAg loss or even seroconversion to anti-HBs benefit from a reduction of replicating HDV RNA in the liver. This is of particular importance as endpoints for new drugs to treat CHD are being developed.

Key point

Treatment of chronic hepatitis D infection has not changed since the 80s and is suboptimal, with poor response rates and limited efficacy.

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Key point

HBsAg clearance is rarely achieved in patients with chronic hepatitis D infection, so it is important to determine whether a reduction in replicating HDV RNA is beneficial.

Histological assessment

Improvement of liver histology has been widely used in the past as proof of efficacy and as a surrogate for reduction in liver-related outcomes in studies of chronic hepatitis B and C. In CHD however, no study has yet shown histological activity to be improved by PegIFNα therapy. No improvement in histologic activity or fibrosis was observed in the HIDIT-1 study,[27] while fibrosis but not activity improved at the end of treatment in the HIDIT-2 study.[28] Part of this may be due to the fact that in clinical studies of patients with CHD the proportion of patients with cirrhosis or advanced liver disease is higher than in trials for other forms of chronic viral hepatitis, even when similar entry criteria are used, which may more frequently lead to inadequate or suboptimal liver biopsies. Given the proportion of patents with cirrhosis, true-cut liver biopsies may be preferred over suction biopsies. As mentioned above, in the HIDIT-2 study, liver fibrosis but not histologic activity improved. The presence of PegIFNα at the time of biopsy may have led to an increased influx of immune cells to the liver, leading to inflammation which may not have been present had biopsies been taken 24 weeks after treatment. Thus, it may be advisable to perform liver biopsies at off-treatment month 6 in studies where PegIFNα is used and effects on histologic activity are sought. However, there was no consensus within the group on the timing of liver biopsy after treatment. We think that histological assessment should still be considered in phase III studies but based on the data and considerations mentioned above, we do not think that liver biopsy should be seen as mandatory. In addition, no study has analysed liver stiffness values during or after IFNα-based therapies and such elastography assessments should be part of future clinical trials.

Considerations based on studies conducted in chronic hepatitis B

Since CHD is a result of the dual infection of HBV and HDV it may seem reasonable to take advantage of the experience gained in treating patients with chronic HBV infection. The ideal endpoint and surrogate marker of treatment efficacy in chronic hepatitis B is HBsAg clearance. HBsAg loss has been associated with an improved long-term clinical outcome in HBV monoinfection,[25] as well as in patients coinfected with HDV.[38,39] However, with the most widely used management strategy, the use of nucleos(t)ide analogues with no or negligible risk of resistance development, this endpoint is rarely achieved. In patients with HBV monoinfection, suppression of serum HBV DNA below the level of detection with a sensitive PCR is considered a valid surrogate of treatment efficacy. This is reasonable since, as pointed out by the recent European Association for the Study of the Liver Guidelines for the management of chronic hepatitis B, the level of HBV replication represents the strongest single predictive biomarker associated with disease progression and the long-term outcome of chronic HBV infection.[25] There is strong evidence, both from prospective randomised studies and from real life cohort studies, that long-term HBV DNA suppression in patients with chronic hepatitis B is associated with a reduction in liver-related complications of cirrhosis, hepatic decompensation and hepatocellular carcinoma, which translate into improved overall survival.[25] Similarly, suppression of HCV replication has been associated with a reduced risk of developing clinical complications of liver disease[26] and with better overall survival.[40] Notably, another treatment approach for HBV is the use of interferons, which have a different mode of action; with this form of therapy, not only undetectable HBV DNA but also HBV DNA below 2,000 IU/ml can be considered a valid endpoint[25] associated with improved outcomes.[25]

Likewise, it is important to note that in CHD, replication of the underlying HDV was found to be the only independent predictor of mortality in a study from Italy.[41] However, it must be stressed that CHD is a different liver disease and that there are fundamental differences in its pathogenesis compared to HBV and HCV.[42] Declines in HDV RNA with IFNα treatment were reported to be associated with improved survival in CHD even if HDV RNA negativity was not achieved, in studies from Turkey[39] and Germany.[38] Farci *et al.*[43] had reported the beneficial effect of high dose conventional IFN over low dose IFN or no treatment groups more than 20 years ago. In a 12 year-follow-up of this initial report the high-dose group was associated with improved survival compared to both the low-dose and no treatment groups.[44] Interestingly, the nested PCR measurements at end of treatment revealed that all patients had detectable HDV RNA. A mean change of HDV RNA from baseline to end of treatment of 2log was observed in the high-dose group and was associated with the reported survival benefit.[44] However, the study by Farci *et al.* was not a randomised controlled clinical trial and the results need to be interpreted with caution. In this context it needs mentioning that no other study has validated the long-term outcome of a 2log decline of HDV DNA at end of treatment. However, in the HIDIT-1 study, more than 50% of patients with undetectable HDV RNA at post-treatment week 24 had detectable HDV RNA at end of treatment. Among those patients, in particular those with high baseline HDV RNA, a more than 2log drop was observed at end of treatment compared to baseline (Yurdaydin & Wedemeyer, unpublished observation).

Endpoints in clinical studies in CHD with new compounds

Currently, 4 new treatment options for CHD are being tested in phase II clinical trials. They target

various steps of the HBV and HDV life cycle.[6,45,46] The hepatocyte entry inhibitor myrcludex B inhibits high affinity binding of HBV and HDV to the entry receptor sodium taurocholate co-transporting polypeptide (NTCP).[47,48] The farnesyl transferase inhibitor lonafarnib interferes with HDV virion assembly.[49] Nucleic acid polymers have been proposed to inhibit HDV virion extrusion from the hepatocytes.[50] Finally, IFNλ is also being developed for HDV as both an immune modulator and an antiviral agent and has been shown to display anti-HDV activity in humanised mice.[51] The first human application of IFNλ in CHD has recently been presented.[23]

First, we will provide a brief description of the available data from phase II studies of new compounds, with special emphasis on their potential contribution to surrogates of treatment efficacy.

Hepatocyte entry inhibitor myrcludex B

This compound has now been tested in several phase II studies. In the proof-of-concept phase II study, 2 mg of subcutaneous myrcludex B administered daily for 6 months, with and without PegIFNα, was assessed in a total of 14 patients (7 per group) with compensated liver disease (including cirrhosis) and compared to PegIFNα monotherapy. The primary endpoint was a >0.5log reduction in quantitative HBsAg levels at week 12 of treatment and none of the patients reached this primary endpoint. Myrcludex B monotherapy led to a mean 1.67$\log_{10}$ reduction in HDV RNA at end of treatment, whereas the combination with PegIFNα was associated with a 2.59$\log_{10}$ reduction.[20] A simulation of a 1-year treatment with placebo, myrcludex B, PegIFNα-2a or their combination was suggestive of a synergistic effect of combination therapy on serum HDV RNA levels. Further, myrcludex B as monotherapy was associated with ALT normalisation in 6 out of 8 patients. In a dose escalating study, 2, 5 and 10 mg daily of myrcludex B in combination with tenofovir for a duration of 6 months was compared with tenofovir monotherapy.[52] This 4-arm study conducted in Russia included 20 patients with CHD-induced compensated liver disease per group. The primary endpoint, a 2log decrease or undetectable HDV RNA at end of treatment was reached by 46, 47 and 77% of patients, with escalating doses of myrcludex B compared to 3% with tenofovir monotherapy. ALT normalised in 43, 50 and 40% of the same patient groups. HBsAg levels were not affected. Myrcludex B was reported to be well tolerated in phase I and II clinical studies. Since NTCP is also a bile salt transporter expressed on hepatocytes, bile acid profiles were assessed in phase I and II studies. Elevation of glycine and taurine-conjugated bile salts was observed without clinical consequences. Further, mild and transient neutropenia, thrombocytopenia and eosinophilia were observed.

Farnesyl transferase inhibitor lonafarnib

Lonafarnib was tested both as monotherapy and in combination with ritonavir (to boost lonafarnib levels in the liver) and with PegIFNα at 3 different sites: in Bethesda at the NIH, in Hannover and in Ankara.[53–55] In these studies, various doses (25 mg to 300 mg of lonafarnib) and combinations were tested for durations of treatment ranging from 3 to 12 months. The LOWR (LOnafarnib With and without Ritonavir) HDV-1 study was a 7-arm single centre pilot study where 20 patients (n = 3 per group) with compensated liver disease including cirrhosis due to CHD received 8 to 12 weeks of treatment with lonafarnib with and without PegIFNα or ritonavir. The primary endpoint was the decline of HDV RNA from baseline to end of treatment. Overall, a combination of low dose lonafarnib with ritonavir or PegIFNα was found to be superior to monotherapy with high dose lonafarnib in terms of combining efficacy with tolerability.[55] whereas the high dose lonafarnib monotherapy + PegIFNα was not well tolerated. The LOWR HDV-2 study aimed to find the optimal treatment regimen and contained a total of 55 patients with compensated liver disease. The primary endpoint of the study was a >2 log decrease in HDV RNA compared to baseline at end of treatment. Patients received different doses of lonafarnib in combination with ritonavir or as triple therapy with the addition of PegIFNα. Lonafarnib at doses of ≥75 mg twice daily in combination with ritonavir were not well tolerated. In combination with 100 mg of ritonavir twice daily, 6 months of lonafarnib 50 mg twice daily had better antiviral efficacy than the 25 mg dosing.[56] Triple therapy with the addition of PegIFNα was associated with the best results and suggestive of synergism.[56] The all oral combination with 24 weeks of lonafarnib 50 mg twice daily led to a >2log decrease of HDV RNA at end of treatment in 6 of 12 (50%) patients. ALT normalisation occurred in 7 out of 10 patients with elevated ALT at baseline. Triple therapy with 24 weeks of twice daily dosing of 25 or 50 mg lonafarnib and 100 mg ritonavir in combination with weekly PegIFNα was associated with a >2 log HDV RNA decrease in 8 of 9 patients and ALT normalisation in all 8 patients with high baseline ALT. HBsAg levels were assessed in both the LOWR HDV-1 and LOWR HDV-3 studies, conducted in Ankara and at the NIH, respectively; For treatment durations of up to 24 weeks, HBsAg levels were not affected with either high dose lonafarnib monotherapy or lonafarnib in combination with ritonavir.[55,57] Interestingly, extending treatment duration to 48 weeks did not appear to increase efficacy. For example, with all oral therapy, a >2log decline in HDV RNA was only observed in 2 out of 5 patients. However, the number of patients is too small for a reasonable assessment. In some patients short-term lonafarnib treatment (3–6 months) was associated with post-

Key point

Four approaches have raised most of the attention, with the efficacy and safety of compounds including an HBV-specific entry inhibitor, a prenylation inhibitor, nucleic acid polymers and interferon lambda currently being tested in phase II trials.

treatment viral and biochemical flares, which were associated with HDV RNA becoming undetectable along with ALT normalisation, as well as suppression of HBV DNA. The mechanism of these favourable post-lonafarnib responses is not entirely understood. At high doses, lonafarnib was associated with dose limiting gastrointestinal adverse events which consisted of anorexia, nausea, diarrhoea and weight loss. At the selected doses, these adverse events were mostly grade 1 according to the common terminology for adverse events criteria. Thus, with both myrcludex B and lonafarnib, a 2log decrease was observed in a sizeable proportion of patients at end of treatment and was mostly associated with ALT normalisation. The latter may be seen as an indirect measure of less necro-inflammation, which is expected to defer liver disease progression.

Nucleic acid polymers

The only phase II study in CHD was conducted in Moldova and included 12 patients with compensated liver disease. In this study, the nucleic acid polymer REP 2139-Ca was given as an intravenous infusion once weekly, with add-on PegIFN starting at week 15 for another 15 weeks.[22] PegIFN alone was then continued as monotherapy for another 33 weeks. Eight patients displayed declines of >2log in HBsAg levels during the monotherapy phase and 5 patients were HBsAg negative at end of treatment. Similarly, patients displayed significant reductions in serum HDV RNA during therapy and 9 patients had undetectable HDV RNA at end of treatment. Eighteen months off treatment, 7 and 5 out of 12 patients had persistent negative HDV RNA and HBsAg, respectively.[58] Nucleic acid polymers have been reported to lead to administration route related side effects such as fever, chills, peripheral hyperaemia. In addition, leukopenia and thrombocytopenia have been reported in some patients. Other side effects include anorexia, hair loss, dysphagia and dysgeusia, observed during treatment in patients with chronic hepatitis B and which were attributed to heavy metal exposure at the trial site.[59] Finally, asymptomatic and transient ALT and aspartate aminotransferase elevations up to the 700 U/L range during REP 2139 monotherapy have been reported.[22,59] There are plans to develop a subcutaneous formula (CY, personal communication with Michel Bazinet).

PegIFN lambda

A phase II study assessing the efficacy and tolerability of 120 μg *vs.* 180 μg of PegIFNλ weekly is ongoing. Pooled interim results of 20 enrolled patients revealed a more than 2log decrease of HDV RNA in 50% and HDV RNA negativity in 40% of patients at 24 weeks of treatment.[23] There were fewer of the adverse events typically seen with INFα but some patients (around 10%) experienced hyperbilirubinemia and increases in ALT and aspartate aminotransferase that were reversible with dose reduction and without any clinical signs of decompensation.

Overall, it is important to note that in all phase II studies with new agents currently tested for CHD, a serum HDV RNA decline of >2log even with detectable viremia was associated with an improvement or even normalisation of ALT levels.[20,22,23,52,55]

Summary and concluding remarks

CHD represents the most severe form of chronic viral hepatitis, for which PegIFNα currently represents the only treatment of demonstrated efficacy, although this efficacy is restricted to a subgroup of patients. Peg-IFNα is associated with significant side effects and has not been approved anywhere in the world for the treatment of CHD. It is a matter of urgency that new treatments become available for CHD. Any new treatment in CHD cannot target HDV RNA polymerase as in other forms of chronic viral hepatitis, since HDV does not possess an HDV RNA polymerase of its own but depends on the polymerase of the host for its replication. This is one reason why it is more challenging to develop antiviral drugs against HDV which show immediate strong potency as is the case in HCV infection.

Future clinical trials need to consider potential viral interactions between HBV and HDV. HDV suppression may lead to HBV reactivation, which in turn can increase liver disease activity.[3,4,55] Thus, combination therapies with nucleos(t)ide analogues suppressing hepatitis B should be considered in future studies in CHD. Further, new studies need to take into account the different modes of action of new compounds. This may affect optimal treatment duration which may differ between compounds. Of the 2 most studied new compounds, it appears that myrcludex B is so far well tolerated and its antiviral efficacy increases with duration of treatment. Thus, myrcludex B may be suitable for prolonged administration, of course with close follow-up for potential adverse events. Myrcludex B monotherapy can also be considered in patients with compensated liver disease but with a somewhat lower platelet count than the usual 90,000 or 100,000/ml cut-offs. Meanwhile, lonafarnib demonstrates more profound early viral responses and appears in some cases to show some waning of antiviral efficacy, particularly after 24 weeks of treatment. Therefore, it may be beneficial to use repeated courses of lonafarnib-based regimens and assess the effect of lonafarnib as a treatment modality applied more than once. Twenty-four weeks of treatment may also be considered in studies where the combination of 2 antiviral agents may have the potential for synergism.

Finally, it must be said that with new compounds the best results have been obtained when they have been used in combination with PegIFNα.

Interferons may therefore continue to be used as the backbone of therapy. The possibility that PegIFNα will be replaced by PegIFNλ exists. However, IFN-free regimens are also needed and future efforts need to encompass studies both with and without interferon. These new studies need to investigate several haematologic, biochemical, serologic and virologic parameters as potential predictors of response, assessed in the past for PegIFNα, but also parameters not assessed such as the baseline-event-anticipation (BEA) score and liver stiffness assessments.[60,61]

Based on data provided here, we propose using, a decline of 2 or more logs of HDV RNA at end of treatment (duration of treatment may vary with different drugs used) as a surrogate marker for initial treatment efficacy in clinical trials. We think that it is reasonable to assume that compounds achieving this antiviral effect can be an important adjunct to other drugs with different antiviral mechanisms in improving the management of CHD, provided that these compounds also possess a reasonable safety profile. HDV RNA levels should be determined by a validated assay with sufficient sensitivity and good performance across all HDV genotypes.[32]

Future studies then need to investigate if not only a relative HDV RNA decline but also a distinct HDV RNA level (*e.g.* <1,000 IU/ml) could be a clinically useful threshold associated with improved clinical outcomes.

Further we propose several secondary endpoints listed in Table 1. These include early virologic responses during therapy, histological evaluation of liver disease activity as well as staging of liver disease (histology activity index [HAI] and fibrosis scores), biochemical disease activity (ALT normalisation at end of treatment and/or off treatment) and HBsAg changes. Finally, we think that important additional exploratory endpoints should be considered (Table 2), which would help to understand the mode of action of distinct investigational compounds, *e.g.* determination of intrahepatic HDV RNA levels, intrahepatic HDV antigen expression, HBV DNA and RNA, hepatitis B core-related antigen levels as well as HBV covalently closed circular DNA quantification. Moreover, non-invasive markers of liver fibrosis and liver stiffness should be assessed. It is well accepted for other liver diseases that respective changes translate into improved long-term clinical outcomes. Since HBV and HDV can be controlled by host immune responses, exploratory studies may include the investigation of innate and adaptive immune responses.

In conclusion, this panel of experts recommends a new virologic surrogate marker (namely a ≥2log drop in HDV RNA), as the target for the assessment of initial treatment efficacy in clinical trials of novel therapies for patients with CHD.

Key point

This panel of experts recommends using a ≥2log drop in HDV RNA at end of treatment as a surrogate marker of initial treatment efficacy in future clinical trials.

Table 1. Treatment goals for clinical trials in HBV/HDV coinfection.

Treatment goals	Parameter	Readout
Virologic efficacy during treatment	Relative HDV RNA decline during treatment compared to baseline levels	HDV RNA (IU/ml) with a validated HDV RNA assay with sufficient sensitivity
Virologic efficacy off treatment	HDV RNA suppression/decline 24 weeks off-treatment and during further long-term follow-up	HDV RNA (IU/ml) with a validated HDV RNA assay with sufficient sensitivity
Serological efficacy-1	HBsAg levels (log declines and loss) at end-of treatment and off treatment	validated quantitative HBsAg assay (IU/ml)
Serological efficacy-2	Seroconversion to anti-HBs at end-of treatment and off treatment	validated quantitative anti-HBs assay (IU/L)
Biochemical efficacy (1)	ALT normalisation at the end of treatment and off-treatment	Validated assays (IU/L)
Biochemical efficacy (2)	Relative ALT declines during treatment and off treatment	Validated assays (IU/L)
Combined virologic and biochemical response-1	HDV RNA decline of 2log (or PCR negativity if baseline viral load is <100 IU/ml) in combination with ALT normalisation at EOT	HDV RNA (IU/ml) with a validated HDV RNA assay with sufficient sensitivity. ALT (IU/L) with standard biochemical assays.
Combined virologic and biochemical response-2	HDV RNA decline of 2log (or PCR negativity if baseline viral load is <100 IU/ml) in combination with ALT normalisation at 24 weeks off treatment and further during long-term follow-up	HDV RNA (IU/ml) with a validated HDV RNA assay with sufficient sensitivity. ALT (IU/L) with standard biochemical assays.
Histological efficacy – grading	Improvement of HAI of at least 2 points	Total Ishak inflammation score (A + B + C + D); 0–18 points
Histological efficacy – staging	No worsening of fibrosis scores	Ishak score (0–6 points)
Safety – Drug-specific AEs	AEs and SAEs	Severity and relation ot study drug
Safety – Disease-specific AEs	HBV and HDV reactivation	HBV DNA, HDV RNA, ALT and other liver function parameters
ProQOLs	Quality of life during and after end of therapy	EQ5, SF-36, etc.

AEs, adverse events; ALT, alanine aminotransferase; cccDNA, covalently closed circular DNA; EOT, end of treatment; HBV, hepatitis B virus; HBsAg, HBV surface antigen; HDV, hepatitis D virus; SAEs, serious AEs.

Table 2. Additional explorative endpoints for clinical trials in HBV/HDV coinfection.

Endpoint	Parameter	Readout
Liver stiffness	Liver elastography	*e.g.* fibroscan, ARFI
Serum biomarkers for inflammation and fibrosis	Established scores (*e.g.* APRI, FIB4, Delta Fibrosis score*) Novel parameters	Serum-/Plasma tests
Intrahepatic virologic response (HDV and HBV)	Intrahepatic HDV RNA, hepatitis D antigen staining, HBV DNA, HBV RNA, HBV cccDNA	Standardized virologic assays
Immune responses	HDV-specific T cells, HBV-specific T cells, NK cell frequency and function, soluble inflammatory mediators	T cell assays, flow cytometry, bead-arrays

AFRI, acoustic radiation force impulse; APRI, aspartate aminotransferase to platelet ratio index; cccDNA, covalently closed circular DNA; FIB4, Fibrosis-4 score; HBV, hepatitis B virus; HDV, hepatitis D virus; ProQOLs: Professional Quality of Life scales.
* Ref. 62.

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Conflict of interest

Dr. Yurdaydin reports personal fees from GILEAD BIOPHARMA, personal fees from AbbVie BIOPHARMA, grants from EIGER BIOPHARMA, outside the submitted work. Dr. Buti. is an advisor/lecturer for AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck, and Novartis. M Cornberg has received lectures and/or consultant fees from AbbVie, Bristol-Myers Squibb, Janssen, Merck/MSD, Abbott, Fujirebio and Roche; grant support from Abbott and Roche; and travel grants from Gilead Science, Bristol-Myers Squibb and Janssen. R Esteban is advisor and speaker for AbbVie, Gilead, and Merck. Dr. Glenn is employed by and owns stock in Eiger. Dr. Gane advises and is on the speakers' bureau for Janssen, Gilead, and AbbVie. Dr. Gish has had Grants/Research Support from AbbVie, Benitec Biopharma, Gilead Sciences, and Merck & Co.; consults/advises AbbVie, Akshaya Pharmaceuticals, AstraZeneca, Bristol-Myers Squibb, Genentech, Gilead, Hoffman- LaRoche, Ionis Pharmaceuticals, Janssen, Merck, Nanogen and Presidio Pharmaceuticals. Dr. Manns has received grant and research support or consulting fees from Roche, BMS, Gilead, Novartis, Merck, Janssen, GSK, AbbVie. R. R.: K.V.K: Gilead, Abbott, Beckman, Boehringer Ingelheim, BMS, Conatus, Ikaria, Intercept, Janssen, Merck, Mochida, Novartis, Vertex. S.R.: Gilead, Meck, AbbVie. Dr. Lampertico serves on the speaking bureau/ and is an advisor for Alnylam, Arrowhead, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck Sharp & Dohme, and Roche. Dr. Urban is co-applicant and co-inventor of patents protecting myrcludex B. Dr. Wedemeyer received honoraria for speaking or consulting from Abbott, AbbVie, BMS, Boehringer Ingelheim, Eiger, Gilead Sciences, Janssen, Merck/MSD, MyrGmbH, Novartis, Novira, Roche Diagnostics, Roche, Siemens, Transgene. Research support from Abbott, BMS, Gilead Sciences, Novartis, Roche Diagnostics and Roche. Drs Abbas, Etzion, Hamid, Heller, Koh, Lurie, Parana and Rizzetto have nothing to disclose.

Authors' contributions

The study was planned and initiated by HW, CY and MPM. The first version of the manuscript was written by CY. Additional versions were first reviewed and modified by HW, MR, SU, JG and CY and subsequently by all authors.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.12.022.

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Author names in bold designate shared co-first authorship

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