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Therapy of Delta Hepatitis

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Delta hepatitis is the less frequently encountered but most severe form of viral hepatitis. Acute delta hepatitis, as a result of coinfection with hepatitis B and hepatitis delta, is rare, but may lead to fulminant hepatitis, and no therapy exists for this form. Chronic delta hepatitis (CDH) mostly develops as a result of superinfection of a hepatitis B surface antigen (HBsAg) carrier with hepatitis delta virus (HDV). In general, HDV is the dominant virus. However, a dynamic shift of the dominant virus may occur with time in rare instances, and hepatitis B virus (HBV) may become the dominant virus, at which time nucleos(t)ide analog therapy may be indicated. Otherwise, the only established management of CDH consists of conventional or pegylated interferon therapy, which has to be administered at doses used for hepatitis B for a duration of at least 1 year. Posttreatment week-24 virologic response is the most widely used surrogate marker of treatment efficacy, but it does not represent a sustained virologic response, and late relapse can occur. As an easy-to-use simple serological test, anti-HDV-immunoglobulin M (IgM) correlates with histological inflammatory activity and clinical long-term outcome; however, it is not as sensitive as HDV RNA in assessing treatment response. No evidence-based rules for treating CDH exist, and treatment duration needs to be individualized based on virologic response at end of treatment or end of follow-up. Effective treatment may decrease liver-related complications, such as decompensation or liver-related mortality. In patients with decompensated cirrhosis, interferons are contraindicated and liver transplantation has to be considered. Alternative treatment options are an urgent need in CDH. New treatment strategies targeting different steps of the HDV life cycle, such as hepatocyte entry inhibitors or prenylation inhibitors, are emerging and provide hope for the future.

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Delta hepatitis is the most severe form of viral hepatitis affecting humans. This applies to both its acute and its chronic form. The causative agent, hepatitis D virus (HDV), discovered more than 35 years ago (Rizzetto et al. 1977), can lead to disease in humans only when it is present with the hepatitis B virus (HBV). As with other dual viral infections, therapy has to be tailored toward the dominant virus, which for the vast majority of cases is the HDV. In the rare instance in which the dominant virus changes (Boyd et al. 2010; Schaper et al. 2010), treating HBV may be considered (Yalçın et al. 2003). As with the other forms of chronic viral hepatitis, such as chronic hepatitis B (CHB) or chronic hepatitis C (CHC), the first effective treatment for chronic delta hepatitis (CDH) was treatment with interferons. First attempts of treating delta hepatitis started in the 1980s with the use of conventional interferons (Farci et al. 1989;

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Rosina et al. 1989; Di Besceglie et al. 1990). Short-term (2–24 wk) interferon treatment was associated in some patients with biochemical and virologic improvement, which, in most cases, reverted after treatment discontinuation, and the need for longer treatment duration became obvious. After a quarter of a century, treatment of CDH has not changed, except that use of conventional interferons has been replaced by pegylated interferons. Major breakthroughs witnessed in the treatment of CHB and CHC, so far, did not occur in the management of CDH. Three main arguments for the lack of progress in the management of CDH can be raised: (1) breakthroughs in treatment of CHB and CHC rely on efforts tailoring treatment to different steps of the life cycle of the hepatitis B and hepatitis C virus, respectively. Because HDV needs HBV for propagation, measures to control HBV infection should have theoretically been effective in treating CDH. This did not occur, however, because the breakthrough in HBV treatment came with the development of nucleos(t)ide analogs (NAs), which revolutionized the management of CHB. However, NAs target the HBV polymerase, a multifunctional protein essential for HBV viral replication (Fung et al. 2011) and have proven to be very effective in inhibiting this enzyme, resulting in the cessation of necroinflammation, progression of liver disease, and positively affecting the natural history of CHB disease (Lok and McMahon 2009; EASL Clinical Practice Guidelines 2012). This has deferred basic and clinical research in targeting other steps of the HBV life cycle, which could have been of benefit for treating HDV as well. On the other hand, the beneficial effect of NAs in CHB monoinfection had no impact on CDH. This was not unexpected because the only HBV function required for HDV propagation is hepatitis B surface antigen (HBsAG) synthesis, and NAs do not target HBsAg synthesis. (2) In contrast to HBV and HCV infection, direct inhibition of HDV replication is not possible. HDV replicates through a double-rolling circling model and also makes use of a polymerase, the cellular RNA polymerase II, with contributory functions of RNA polymerase I and III (Greco-Stewart et al. 2009; Taylor 2012), all of which are host polymerases and should, therefore, not be targeted because of toxicity. (3) HDV is becoming an infrequent problem despite hot spots of hyperendemic disease mainly affecting areas of the world with low socioeconomic status (Wedemeyer and Manns 2010; Hughes et al. 2011). The low financial reward is unfortunately a likely explanation for the lack of interest by major pharmaceutical companies in developing drugs for CDH, and the challenge of drug development relies now more on academic institutions. However, management of CDH is likely to enter a new area very soon because the first human trials on the use of treatment strategies targeting different steps of the HDV life cycle are ongoing and results are expected to be disclosed soon.

TREATMENT OF ACUTE DELTA HEPATITIS

Acute delta hepatitis (ADH) resembles a typical self-limited hepatitis that is clinically and histologically indistinguishable from hepatitis B or other types of viral hepatitis. It may, however, lead to a biphasic type of hepatitis, possibly related to sequential expression of the two viruses that have been observed both in early chimpanzee studies (Rizzetto et al. 1980) and prospectively in injecting drug users (Caredda et al. 1985). The acute hepatitis can clinically range from mild hepatitis to fulminant hepatitis leading to death. Early studies both from the United States and Europe had clearly shown that coinfection of HBV HDV more often leads to severe or fulminant hepatitis compared to patients monoinfected with HBV (Smedile et al. 1982; Govindarajan et al. 1984; Caredda et al. 1987). However, a more recent study from Spain (Buti et al. 2011) reported the development of fulminant hepatitis attributable to HBV HDV in only two (1.7%) out of 115 patients, and may suggest that, with the slower turnover of HDV in the community, acute fulminant HDV may also be much less frequently encountered. This is good news, as no therapy of proven efficacy exists for the treatment of ADH. In this context, trisodium phosphonoformate (foscarnet) and interferon (IFN)-α have been tested in the past as possible treatment regimens in ADH. Three patients with fulminant hepatitis D were given

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foscarnet, an inhibitor of HBV replication, and each of them recovered (Niro et al. 2005b). However, in vitro data indicate that foscarnet actually enhances HDV replication; thus, its clinical success may have been a fortuitous effect (Niro et al. 2005b). Foscarnet was not further tested; its poor oral bioavailability and nephrotoxicity have been discouraging (Wagstaff and Bryson 1994; Niro et al. 2005b). IFN-α was associated with dismal results in patients with fulminant hepatitis D (Sanches-Tapias et al. 1987).

TREATMENT OF CHRONIC DELTA HEPATITIS

Treatment with Interferons

The only evidence-based effective therapy for CDH is treatment with interferons. Throughout the years, many drugs have been tested for CDH, but none of them proved to be effective. The first attempts date back to the 1980s when immunosuppressive agents, such as prednisone and azathioprine, and immunostimulants, such as levamisole, were tested at a time when there was more or less only indirect evidence of CDH being an immune-mediated disease (Actis et al. 1987). None of these three agents proved to be effective (Arrigoni et al. 1983; Rizzetto et al. 1983). Although not as vigorously investigated as CHB or CHC, there is now accumulating evidence that CDH is essentially an immune-mediated disease (Grabowski and Wedemeyer 2010; Grabowski et al. 2011; Karatayli et al. 2014; Lunemann et al. 2014). However, there may be exceptions to this. Genotype-3 HDV has been reported to lead to a particularly severe form of delta hepatitis, whereas histologic findings are not reminiscent of an immune-mediated liver injury, and a cytopathic role for genotype 3 has been attributed (Casey et al. 1996).

The first studies with interferons were performed in the late 1980s. Several studies in the late 1980s and 1990s suggested that treatment duration should probably not be shorter than 1 yr, and that IFN-α-2a or IFN-α-2b should be given at a dose of 9–10 million units thrice weekly (Rizzetto 2009; Yurdaydin et al. 2010). A list of controlled clinical trials (Rosina et al. 1991; Farci et al. 1994; Madejon et al. 1994; Gaudin et al. 1995; Günşar et al. 2005; Canbakan et al. 2006; Yurdaydin et al. 2008) on the use of IFN-α-2a or IFN-α-2b for a duration of 1 yr is provided in Table 1. With the advent of pegylated interferon, more recent studies have made use of this type of therapy (Castelnau et al. 2006; Erhardt et al. 2006; Niro et al. 2006; Gheorge et al. 2011; Örmeci et al. 2011; Wedemeyer et al. 2011, 2014; Karaca et al. 2013; Abbas et al. 2014). Studies performed with pegylated interferon for a duration of at least 1 and up to 2 yr are summarized in Table 2. Response to treatment is assessed in the majority of publications at posttreatment week 24, and patients who are HDV RNA negative at this time point are considered to have a virologic response to treatment. Conventional or pegylated interferon therapy for 1 yr leads to virologic response rates of around 25%, which clearly underlines the need for treatment optimization and alternative treatment options.

Before commenting on responses to treatment, several issues need to be discussed. The first issue concerns valid surrogate markers of treatment efficacy. As with hepatitis B, HBsAg clearance would be an ideal surrogate marker of treatment efficacy. However, this is very rarely achieved, at least in a reasonable time frame. Thus, posttreatment month-six HDV RNA undetectability has been regarded as a reasonable surrogate of treatment efficacy, and by many as an indication for sustained virologic response, similar to treatment assessment in patients with chronic hepatitis C. However, Heidrich et al. (2014) was able to show that, on long-term follow-up of 16 posttreatment virologic responder patients of the Hep Net International Delta Intervention Trial (HIDIT)-1 study, nine patients tested HDV RNA positive at least once during 5 yr of follow-up. Rizzetto amd Smedile suggested that relapse after apparent successful treatment in CDH might be because of the high infectivity of HDV in the setting of established HBV infection (Rizzetto and Smedile 2015). HDV may remain infective at very low titers, as has been shown in early studies using chimpanzees in which infectious serum diluted as much as 10^{11} times was still able to transmit HDV to HBsAg-positive chimpanzees (Ponzetto et al.

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Table 1. Controlled clinical trials of the use of interferons for the duration of at least 1 year

References	Treatment schedule	*N*	EOT VR	EOFU VR
Rosina et al. 1991	IFN-α-2b, t.i.w., 5 MU/m^2 × 4 mo + 3 MU/m^2 × 8 mo	31	45%	Not applicable
	No treatment	30	27%	Not applicable
Farci et al. 1994	IFN-α-2a, t.i.w., 9 MU/m^2 × 12 mo	14	71%	43%
	IFN-α-2a, t.i.w., 3 MU/m^2 × 12 mo	14	36%	14%
	No treatment	13	0%	8%
Gaudin et al. 1995	IFN-α-2b, t.i.w., 5 MU/m^2 × 4 mo + 3 MU/m^2 × 8 mo	11	64%	18%
	No treatment	11	36%	Not applicable
Madejon et al. 1994	IFN-α-2a, t.i.w., 18 MU × 6 mo + 9 MU × 1 mo + 6 MU × 1 mo + 3 MU × 4 mo	16	31%	Not applicable
	IFN-α-2a, q.d., 3 MU × 3 mo + 1.5 MU × 9 mo	16	25%	Not applicable
Günşar et al. 2005	IFN-α-2a, t.i.w., 9 MU × 24 mo	10	50%	20%
	IFN-α-2a, t.i.w., 9 MU × 24 mo + ribavirin, 1-1.2 g, q.d.	21	52%	24%
Canbakan et al. 2006	IFN-α-2b, t.i.w., 10 MU × 12 mo	12	42%	17%[a]
	IFN-α-2b, t.i.w., 10 MU × 12 mo + lamivudine	14	64%	29%[a]
Yurdaydin et al. 2008	IFN-α-2a, t.i.w., 9 MU × 12 mo	8	50%	50%
	IFN-α-2a, t.i.w., 9 MU × 12 mo + lamivudine	14	50%	36%

EOT, End of treatment; EOFU, end-of-treatment follow-up; VR, virologic response; IFN, interferon; t.i.w., three times a week; MU, megaunits; q.d., every day.

[a]End of 6–12 months treatment-free follow-up (FU) except where mean FU was 3.1 years.

Table 2. Studies with pegylated interferon

References	Treatment schedule	*N*	EOT VR	EOFU VR
Niro et al. 2006	Peg-IFN-α-2b, 1.5 μg/kg, q.w. × 18 mo	16	19%	25%
	Peg-IFN-α-2b, 1.5 μg/kg, q.w. × 18 mo + ribavirin, 1-1.2 g, q.d. × 12 mo	22	9%	18%
Castelnau et al. 2006	Peg-IFN-α-2b, 1.5 μg/kg, q.w. × 12 mo	14	57%	43%[a]
Erhardt et al. 2006	Peg-IFN-α-2b, 1.5 μg/kg, q.w. × 12 mo	12	17%	17%
Wedemeyer et al. 2011	Peg-IFN-α-2a, 180 μg, q.w. × 12 mo	29	24%	26%
	Peg-IFN-α-2b, 180 μg, q.w. × 12 mo + adefovir, 10 mg, q.d.	31	23%	31%
Gheorge et al. 2011	Peg-IFN-α-2b, 1.5 μg/kg, q.w. × 12 mo	48	33%	25%
Örmeci et al. 2011	Peg-IFN-α-2b, 1.5 μg/kg, q.w. × 24 mo	9	56%	44%
	Peg-IFN-α-2b, 1.5 μg/kg, q.w. × 12 mo	7	57%	100%
Abbas et al. 2014	Peg-IFN-α-2a, 180 μg, q.w. × 12 mo	104	42%	23%
Karaca et al. 2013	Peg-IFN-α-2a, 180 μg, or peg-IFN-α-2b, 1.5 μg/kg, q.w. × 24 mo	32	50%	47%[b]
Wedemeyer et al. 2014	Peg-IFN-α-2a, 180 μg, q.w. × 24 mo	61	33%	21%
	Peg-IFN-α-2a, 180 μg, q.w. × 24 mo + tenofovir, 300 mg, q.d.	59	48%	29%

Peg, Pegylated; q.w., every week.

[a]End of 6 mo treatment-free FU except where median FU was 16 mo.

[b]End of 6 mo treatment-free FU except where median FU was 6–60 mo.

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1987). It is noteworthy that, in CDH, patients who may be HDV RNA positive at the end of treatment may become HDV RNA negative during posttreatment follow-up (Niro et al. 2006; Wedemeyer et al. 2011, 2014), further suggesting that any treatment end point transferred from the chronic hepatitis C literature is unlikely to be useful for HDV. On the other hand, in the study by Heidrich et al. (2014), none of the patients who had a virologic response at posttreatment week 24 developed a clinical event defined as liver-related mortality, liver transplantation, the development of hepatocellular cancer (HCC), or hepatic decompensation at long-term follow-up. All four patients who lost HBsAg during long-term follow-up had a posttreatment virologic response. This suggests that posttreatment week-24 virologic response may still be clinically useful, and may be used as a treatment-assessment tool; however, the phrase "sustained virologic response" shall not be used.

Another important issue for consideration is the reliable measurement of serum HDV RNA. The lack of a standardized assay for HDV RNA measurements has been a significant problem in the studies mentioned to date. Even within reference laboratories, discordant results with the same serum samples have been observed (Le Gal et al. 2010). Fortunately, a World Health Organization (WHO) standard for HDV RNA measurement recently became available (Chudy et al. 2013), which will hopefully overcome the confusion related to HDV RNA measurements. The lack of standardized HDV RNA assays, so far, may to some extent explain the variations in the rates of sustained virologic responses reported in past studies as well as in recent studies with pegylated interferons (Castelnau et al. 2006; Erhardt et al. 2006; Niro et al. 2006; Wedemeyer et al. 2011). Additional factors contributing to the divergent virologic response rates of 17%–43% in studies with pegylated interferon are the small sample sizes, the different drop-out rates affecting intention-to-treat analyses, and possible differences in baseline host and viral factors.

CDH is the most severe form of chronic viral hepatitis and, as such, patients with cirrhosis are much more frequently encountered in clinical trials with interferons. In the HIDIT-1 study, response to treatment of patients with advanced liver disease was found to be similar to that of nonadvanced liver disease (Kabaçam et al. 2012a). According to the results of the recently completed HIDIT-2 study, by far the largest study ever performed in CDH (Wedemeyer et al. 2014), patients with cirrhosis actually responded better than those with mild disease. However, it needs to be pointed out that, in the HIDIT-1 study, out of 60 patients receiving pegylated interferon, there were two cases of hepatic decompensation, one case of tuberculosis reactivation, and, unfortunately, one fatality, all occurring among the 31 patients with advanced liver disease. On the other hand, in a study from Turkey with only treatment-naïve patients, the results were different (Günşar et al. 2005). In this study, none of the eight cirrhotic patients had a virologic response, whereas seven of 23 noncirrhotic patients had a virologic response ($p = 0.07$). It should be noted that patients with compensated cirrhosis represent a heterogeneous clinical spectrum (Everson et al. 2006) with variable degrees of portal hypertension; this differential feature is often not considered in the evaluation of response to therapy.

In chronic hepatitis C, accumulated evidence has indicated a difference in response to treatment between treatment-naïve patients and treatment-experienced patients. Patients who had a partial response or who had no response (null responder patients) to a previous course of treatment with pegylated interferon and ribavirin, respond to a second course less well compared to treatment-naïve patients. In contrast, in patients who have had a virologic response at end of treatment but then relapsed after treatment discontinuation, response to a subsequent course is better (EASL Clinical Practice Guidelines 2011; Ghany et al. 2011). Whether treatment-experienced patients respond to treatment as well as treatment-naïve patients is an unresolved issue in CDH. In a study from Italy, being treatment naïve at baseline was an independent predictor of treatment efficacy (Niro et al. 2006). However, in the two largest studies performed in CDH, the HIDIT-1 and HIDIT-2 studies, no difference in posttreatment week-24 virologic response was observed

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between treatment-naïve patients and treatment-experienced patients (Wedemeyer et al. 2011, 2014). In the only study in which this comparison was specifically addressed, no difference between treatment-naïve and treatment-experienced patients was observed in their response to treatment (Yurdaydin et al. 2008). It is likely that a certain bias exists in such trials in the context that patients who responded to a previous course and then relapsed would likely be more willing to receive another course of treatment compared to those who had not responded to treatment.

Treatment with interferons is associated with the burden of weekly injections and a plethora of side effects. To predict who will respond to treatment is an unmet need in CDH. Interleukin-28B polymorphisms do not appear to predict treatment response (Visco-Comandini et al. 2014; Yilmaz et al. 2014). A recent study on HDV RNA and HBsAg kinetics during pegylated interferon therapy has shown a biphasic HDV RNA decline with a first phase lasting a median of 25 days to be followed by a second phase with slower or no decline (Guedj et al. 2014). These data suggest that stopping rules can be developed for pegylated interferon therapy in CDH. An on-treatment HDV RNA measurement can be used for treatment-response prediction (O Keskin, H Wedemeyer, A Tüzün, et al., unpubl.). In the HIDIT-1 study, earlier on-treatment time points could not be evaluated as those data were not available, but in a similar analysis of the HIDIT-2 study, earlier on-treatment time points did not perform as well as month-six HDV RNA measurements (Wöbse et al. 2014). On-treatment week-24 HDV RNA negativity had a positive predictive value (PPV) of 100% for post-treatment week-24 viral response (O Keskin, H Wedemeyer, A Tüzün, et al., unpubl.). Although these data confirmed the results of two previous studies (Castelnau et al. 2006; Yurdaydin et al. 2008), it is based on only five patients. On the other hand, a less than 1 log decline of HDV RNA at month six had a modest negative predictive value (NPV) of 75% for posttreatment week-24 virologic response (O Keskin, H Wedemeyer, A Tüzün, et al., unpubl.). Currently, an early stopping rule recommendation cannot be made because of insufficient "power" in the above analyses.

Treatment with pegylated interferon in CDH should be for a duration of at least 1 yr, although optimal treatment duration is still not known. In several clinical studies, 2 yr of conventional or pegylated interferon treatment did not appear to provide higher virologic response rates compared to 1 yr of treatment (Di Marco et al. 1996; Günşar et al. 2005; Yurdaydin et al. 2007; Örmeci et al. 2011). However, these were small clinical studies, and any conclusion based on those studies risks being misleading. The recently completed HIDIT-2 study, in which pegylated interferon–based treatment was administered for 2 yr, did not appear to increase posttreatment virologic response rates and was associated with high relapse rates after treatment cessation (Wedemeyer et al. 2014). However, beyond expert opinion, there is data, although limited, to suggest that patients may need treatment durations beyond 1 yr (Lau et al. 1999a; Kabaçam et al. 2011; Heller et al. 2014), but the length of treatment duration will probably be determined on an individual patient basis. Cumulative treatment durations up to 10 or 12 yr have been reported (Lau et al. 1999a; Kabaçam et al. 2011). The need for a prolonged course of treatment with interferons is not surprising because, in assessing HDV RNA kinetics during pegylated interferon therapy, the estimated loss of infected cells, corresponding to the slow second phase of HDV RNA decline, was reported to be 10–20 times lower than what was found in HCV- or HBV-monoinfected patients treated with interferon, respectively (Neumann et al. 1998; Ribeiro et al. 2010; Guedj et al. 2014). Further, a long delay of a median of 8.5 days was observed before pegylated interferon had a significant effect in reducing HDV RNA levels in CDH (Guedj et al. 2014), again in contrast to the situation in HBV or HCV infection where this delay is only between 10 to 20 h (Dahari et al. 2010; Ribeiro et al. 2010). These data complement in vitro data that have consistently revealed a lack of effect of interferons on HDV RNA in cultured cells (Ilan et al. 1992; Chang et al. 2006) and that HDV itself might directly inhibit IFN-α signaling (Pugnale et al. 2009). A recent study

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has shown that interferon can delay HDV entry into hepatocytes (Han et al. 2011). This suggests that the effectiveness of interferon therapy may involve blocking HDV spread to other hepatocytes rather than acting as a direct antiviral agent, which further rationalizes the need of long-term interferon treatment in CDH.

Can other parameters be used beyond HDV RNA measurements to assess treatment efficacy? The clearance of HBsAg represents the ultimate treatment end point, and quantification of HBsAg could theoretically provide additional information. This is supported by data that show that successful interferon treatment is associated with a decrease not only in serum HDV RNA but also in quantitative HBsAg levels (Manesis et al. 2007). Further, a correlation has been observed between serum HDV RNA and HBsAg levels, but not with HBV DNA levels (Zachou et al. 2010). In the assessment of HDV RNA and HBsAg kinetics during pegylated interferon treatment, HBsAg kinetics paralleled the second phase of HDV RNA decline, and none of the patients with a flat second phase in HDV RNA and HBsAg developed a virologic response (Guedj et al. 2014). In a study aimed to develop stopping rules, on-treatment week-24 quantitative HBsAg levels predicted end-of-treatment and posttreatment week-24 virologic response by univariate analysis. However, quantitative HBsAg levels failed to be an independent predictor of treatment efficacy in this analysis (O Keskin, H Wedemeyer, A Tüzün, et al., unpubl.). At this stage, no firm recommendation of the use of quantitative HBsAg for treatment assessment can be made, and future studies will be needed to understand the impact. Another potential easy-to-use parameter is a serologic marker, namely, anti–HDV IgM. The levels of anti–HDV IgM correlate with histological inflammatory activity and clinical long-term outcome. It is not as sensitive a measurement as HDV RNA in assessing treatment response, but patients who are anti–HDV IgM negative do not appear to develop on long-term follow-up a clinical event, such as hepatic decompensation, HCC, require liver transplantation, or suffer a liver-related death (Mederacke et al. 2012a; Wranke et al. 2014).

Several treatment algorithms have been proposed for CDH with interferons (Wedemeyer and Manns 2010; Yurdaydin et al. 2010, 2012; Hughes et al. 2011; Ciancio and Rizzetto 2014). Out of four, only one proposes a liver biopsy before commencing treatment. Two propose adding a nucleos(t)ide analog if HBV DNA is >2000 IU/mL. All algorithms base their pretreatment and end-of-treatment assessments on serum HDV RNA, two with and two without ALT assessments, while one algorithm recommends to monitor quantitative HBsAg levels as well. All four algorithms recommend 1 yr of treatment, but propose to prolong treatment if HDV RNA levels remain detectable, or when relapse occurs after treatment discontinuation. Recently, Wedemeyer and colleagues proposed the so-called baseline-event-anticipation (BEA) score for treatment assessment (Calle Serano et al. 2014). The proposed algorithm developed by our group is depicted in Figure 1. It is important to check every patient with HBsAg positivity for HDV using anti-HDV serology. This is even more important in CHB patients with active disease. Overall, our group believes that a patient with HDV viremia and elevated transaminases should be started on pegylated IFN-α-2a or α-2b for the duration of 1 yr (Yurdaydin et al. 2012). If, at the end of treatment, HDV RNA is negative, treatment can be stopped and the patient followed closely posttreatment. In case of virologic relapse, treatment for another year is advised, especially when associated with elevated transaminases. After the second year of treatment, we suggest that the patient should be assessed with the same approach. In patients who show a partial virologic response after 1 yr of treatment (i.e., >2 $\log_{10}$ copies/mL decline of HDV RNA), it is advised to continue treatment for a second year. Effective treatment of CDH appears to favorably affect disease progression (Farci et al. 2004; Manesis et al. 2013).

COMBINATION TREATMENT WITH INTERFERONS AND NUCLEOS(T)IDE ANALOGS

Combination treatments with interferons and antivirals against HBV have been explored

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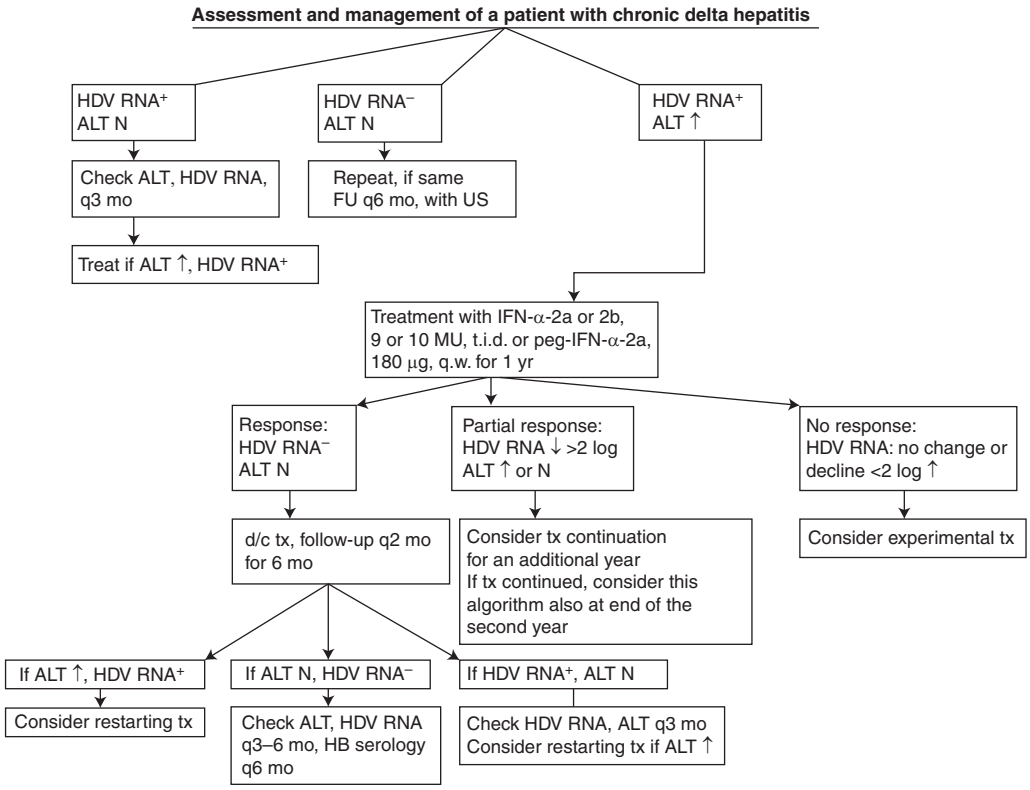


Figure 1. Suggested algorithm for the treatment of chronic delta hepatitis. HDV, Hepatitis D virus; q2/3/6 mo, every 2/3/6 months; peg, pegylated; IFN, interferon; t.i.d., three times a day; q.w., every week; d/c, discontinue; N, Normal; ↑, increased; FU, follow-up; US, ultrasound; tx, treatment; ALT, alanine aminotransferase.

with the hope of enhancing response rates. Unfortunately, these attempts have been disappointing. No increase in virologic response was observed with the combination of IFN-α with lamivudine (Wolters et al. 2000; Canbakan et al. 2006; Yurdaydin et al. 2008). Likewise, the combination of conventional or pegylated interferon with ribavirin (Günşar et al. 2005; Kaymakoğlu et al. 2005; Niro et al. 2006) and the combination of adefovir with pegylated interferon (Wedemeyer et al. 2011) did not increase the virologic response compared to interferon monotherapy. However, the combination of pegylated interferon with adefovir was more effective compared to interferon monotherapy in reducing HBsAg levels (Wedemeyer et al. 2011). In the recently completed HIDIT-2 study, the impact of HBsAg decline was further assessed by comparing the combination of pegylated interferon with tenofovir versus pegylated interferon monotherapy (Wedemeyer et al. 2014). In contrast to the pegylated interferon–adefovir combination, HBsAg decline was not different between the combination and monotherapy arms, and virologic response was also similar between groups. Thus, currently, the combination of pegylated interferon with NAs does not appear to provide additional benefit over monotherapy. However, some experts advocate the use of combination treatment in patients with high HBV viral load in their treatment algorithms (Wedemeyer and Manns 2010; Hughes et al. 2011). Further controlled studies are clearly needed.

NA TREATMENT OF CDH

The first NA tested for the treatment of CDH was ribavirin for which activity against both RNA and DNA viruses had been reported (Patterson

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and Fernandez-Larsson 1990). Ribavirin-induced inhibition of HDV replication in cultured primary woodchuck hepatocytes had been described (Choi et al. 1989). However, no virologic or biochemical effect was observed in human CDH when ribavirin was used (Garripoli et al. 1994). With the advent of NA therapy for the treatment of CHB, it was hoped that NAs would also have an effect on CDH, based on the assumption that by treating HBV the helper function exerted by this virus to support HDV infection would be abolished with a therapeutic benefit also for patients with CDH. Several NAs have been tested in CDH for the last 15 years. Unfortunately, neither the less potent NAs, such as famciclovir (Yurdaydin et al. 2002) and adefovir (Wedemeyer et al. 2011), nor the intermediately potent lamivudine (Yurdaydin et al. 2008; Lau et al. 1999b; Niro et al. 2005a) and the more potent NA, such as entecavir (Kabaçam et al. 2012b), had a virologic or biochemical effect. The main reason for the disappointing results is that NAs cause inhibition of HBV DNA synthesis, but not the production of HBsAg, which is the primary function of HBV in support of the HDV life cycle. On the other hand, lamivudine is associated with resistance and the rtM204V and rtM204I substitutions in the polymerase gene lead to change in the overlapping *S* gene, such as the *sW196L/S*, which inhibits HDV secretion (Vietheer et al. 2005). The consequence of this compromised HDV secretion is unclear.

More promising results were observed in HDV patients coinfected with the human immunodeficiency virus (HIV); a significant decline of HDV RNA was observed in 13 of 16 patients treated mainly with tenofovir for a median of 6 yr (Sheldon et al. 2008), although the reason for this benefit is not clear. This study differed from the earlier studies using other NAs on two aspects: (1) the duration of treatment was much longer; and (2) the study population was coinfected with HIV. Both aspects probably need to be considered for a valid interpretation of this study. Prolonged treatment with tenofovir may have contributed indirectly by affecting HBsAg production through an overall decrease of HBV titers and perhaps a reduction in infected hepatocytes owing to the prolonged inhibition of HBV DNA synthesis (Wursthorn et al. 2006). A significant decline of quantitative HBsAg levels during long-term treatment with NAs in HBeAg-negative HBV monoinfection would also support such reasoning (Manesis et al. 2011). On the other hand, another issue that needs to be considered is the effect of immune restoration during years of treatment with antiretroviral treatment of HIV infection. In a study on patients with HBV HIV coinfection, patients treated with antiretroviral treatment for a median duration of 2 yr, mean HBsAg levels decreased, whereas, in patients not receiving such treatment, HBsAg levels increased (Arendt et al. 2012). Further, among treated patients, those who had a decline in HBsAg levels had significantly higher baseline CD4 cell counts and also higher CD4 counts at the last follow-up compared to those whose HBsAg levels did not change (Arendt et al. 2012). Interestingly, in the study by Sheldon et al. (2008), a positive correlation was observed between serum HDV RNA and serum HBV DNA, which is different from HDV infection without HIV (Zachou et al. 2010), and may suggest immune pressure against both viruses. All of these data lend support for the notion that the beneficial effect of prolonged NA treatment in HDV HIV infection may be a consequence of immune restoration. Importantly, long-term studies of prolonged NA treatment in CDH without HIV infection still need to be completed.

An NA that raised particular interest in CDH was clevudine because, in the woodchuck hepatitis model, it inhibited the production of surface antigen in a dose-dependent manner (Peek et al. 2001) and, in a preliminary study, it was able to significantly decrease HDV RNA in woodchucks infected with HDV (Casey et al. 2005). Unfortunately, in a small pilot study in humans, clevudine was found to be ineffective (Yakut et al. 2010), and its further development was put on hold owing to the development of mitochondrial toxicity (Kim et al. 2009).

In HBV HDV coinfection, HDV is usually the dominant virus and represses HBV production, resulting in low or undetectable levels of HBV DNA in the blood (Schaper et al. 2010; Kabaçam et al. 2014). However, dynamic

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shifts of the dominant virus over time are also possible, and HBV levels increase and exceed those of HDV (Boyd et al. 2010; Schaper et al. 2010). Theoretically, NA could be effective in patients with CDH where HBV becomes the dominant virus (Yalçın et al. 2003; Kabaçam et al. 2012b). Further studies are needed to address these issues.

OTHER THERAPIES

Two pilot studies reported on the use of thymus-derived peptides for 6 mo with twice weekly intramuscular injections in CDH. Thymosin-α1, a 28-amino-acid polypeptide isolated from the bovine thymus extract thymosin fraction 5, was tested in a small randomized study; one of five patients became HDV RNA negative and another patient who was HDV RNA negative at baseline but had HDAg in liver tissue achieved a biochemical response (Zavaglia et al. 1996). In another study, thymic humoral factor-γ2, a thymus-derived synthetic octapeptide, was used in 11 patients; HDV RNA became undetectable in three of eight patients with HDV RNA detectable at baseline, of whom two had a virologic relapse (Rosina et al. 2002). Thymus-derived peptides are believed to have a variety of immunomodulatory effects (Katorza et al. 1987; Gosso et al. 1992), and beneficial effects were reported using a combination of thymic humoral factor-γ2 with IFN-α in chronic hepatitis B (Farhat et al. 1995); however, no such combination has been tested in CDH.

TREATMENT OF PATIENTS WITH HDV-INDUCED DECOMPENSATED CIRRHOSIS

Interferons are contraindicated in patients with decompensated cirrhosis. NAs may be considered as a bridge for liver transplantation. Liver transplantation is the only treatment option for patients with end-stage liver disease. Post-liver transplantation HDV recurrence was less frequent and survival was better compared to HBV alone before the era of modern HBV prophylaxis for managing HBV recurrence (Samuel et al. 1993). As with HBV monoinfection, combination prophylaxis with hepatitis B immune globulin and NAs is the gold standard for prevention of recurrence and provides excellent recurrence-free survival rates in patients transplanted for HDV-induced liver disease (Grellier et al. 1996; Markowitz et al. 1998). One note of caution should still be applied; a recent study has shown HDV immunostaining up to 19 mo after liver transplantation (Mederacke et al. 2012b). This latency of HDV in the liver, reported also previously (Ottobrelli et al. 1991; Samuel et al. 1995), may increase the risk of rescuing HDV infection in case of reappearance of HBV, and patients with HDV may, therefore, not be suitable candidates for early hepatitis B immune globulin withdrawal after liver transplantation (Mederacke et al. 2012b).

EMERGING TREATMENTS IN CDH

It is likely that treatment in CDH will enter a new era in the foreseeable future where several steps of the HDV life cycle will be targeted. They include (1) attachment of HDV to the hepatocyte cell membrane; (2) uncoating in the cytoplasm and targeting of the ribonucleoprotein complex to the nucleus; (3) replication of new transcripts including mRNAs to form hepatitis delta antigen from antigenomic RNA and export of newly formed ribonucleoprotein complexes to the cytoplasm; (4) virion assembly in the cytoplasm, and (5) export of the new virion from the hepatocyte via the *trans*-Golgi network (Fig. 2) (Glenn 2005; Taylor 2006; Hughes et al. 2011). Two approaches have reached clinical stages of development and are currently being tested in phase-2 human trials. They involve interventions with virus attachment to the hepatocyte via hepatocyte entry inhibitors and with HDV virion assembly via prenylation inhibitors.

HEPATOCYTE ENTRY INHIBITORS

As HBV surface proteins provide the envelope for HDV, it has been considered that both HBV and HDV share the same receptor for cellular attachment and entry, which appears to be indeed the case. Several studies have consistently

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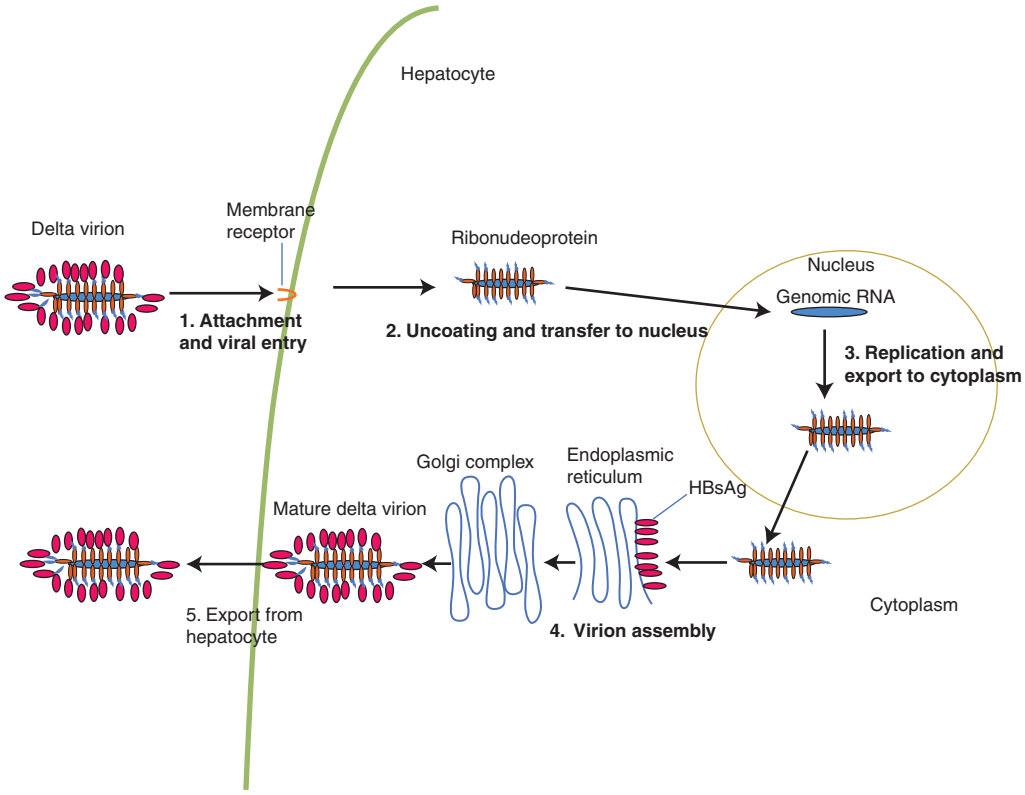


Figure 2. The hepatitis delta virus life cycle and potential targets for therapy. (1) Attachment to hepatocyte: the hepatitis B virus large antigen (or preS1) is crucial for attachment. (2) Uncoating and translocation to nucleus: transport to the nucleus is mediated most likely by the small delta antigen through its nuclear localizing signals. (3) Viral replication: viral replication occurs through a rolling circle model similar to plant viroids; of note is that HDV does not possess a polymerase of its own but uses RNA polymerase II of the host for this purpose. (4) Virion assembly: newly replicated HDV RNA and associated delta antigens are incorporated into an enveloped particle. (5) Export of the mature virion from the hepatocyte.

shown that the large (L) surface protein of the HBV envelope is important for the step of cellular attachment of both HBV and HDV (Barrera et al. 2005; Engelke et al. 2006). Studies have also highlighted the importance of the integrity of the amino-terminal 77 amino acids in the preS1 domain and that myristoylation of glycine in the preS1 domain may be crucial for cellular attachment (Gripon et al. 1995; Blanchet and Sureau 2007). Abolishment of HBV infection by interfering with these properties has been shown both in vitro (Gripon et al. 1995; Blanchet and Sureau 2007) and in vivo (Petersen et al. 2008; Lütgehetmann et al. 2012). The first proof-of-concept human study showed that the HBV HDV entry inhibitor Myrcludex B was well tolerated and that 6 mo daily subcutaneous administration led to >1 $\log_{10}$ reduction in HDV RNA in six of seven patients with CDH (Alexandrov et al. 2014). At week 24, one patient became HDV RNA negative while, with combination of Myrcludex B with pegylated interferon, five of seven patients became HDV RNA negative. Recently, sodium taurocholate cotransporting polypeptide (NTCP) has been identified as the functionally active specific receptor for HBV HDV (Yan et al. 2012) and is the target of Myrcludex B. This discovery will pave the way for drug development and screening for HDV HBV hepatocyte entry inhibition by using NTCP-based cell culture systems (Ni et al. 2013).

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PRENYLATION INHIBITORS

An important step of the HDV life cycle is virion assembly in which the newly formed ribonucleoprotein complexes consisting of delta RNA and antigen are covered by HBV envelope proteins. Prenylation of the large delta antigen is necessary for this step. The large delta antigen contains at its carboxyl terminal a cysteine residue containing a four-amino-acid motif that serves as a substrate for prenyltransferases (Glenn et al. 1992). Prenylation renders the protein more lipophilic and may help target large delta antigens to cellular membranes containing HBsAg. Two types of prenylation inhibitors are known, the farnesyltransferase and geranylgeranyltransferase inhibitors, of which the former is specific for HDV (Glenn 2005). Prenylation inhibitors specifically abolished HDV-like particle production in vitro (Bordier et al. 2002) and in vivo (Bordier et al. 2003). In a phase-2a double-blind, randomized, placebo-controlled clinical trial, 14 CDH patients received twice a day orally 100 mg or 200 mg of the prenylation inhibitor lonafarnib for a duration of 28 d (Koh et al. 2014). The mean log HDV RNA reduction at day 28 from baseline was −0.12 IU/mL with placebo ($p = 0.31$), −0.74 IU/mL with the lower dose ($p = 0.02$), and −1.60 IU/mL with the higher dose of lonafarnib ($p < 0.0001$).

RNA INTERFERENCE

RNA interference (RNAi) mediates sequence-specific inhibition of gene expression via a posttranscriptional gene-silencing mechanism (Scherr and Eder 2007). ARC-520, a novel, short interfering RNA (siRNA)-containing, liver-targeted therapeutic for treatment of CHB, designed to reduce all HBV transcripts via RNA interference, was used in a randomized, double-blind, placebo-controlled fashion in HBeAg-negative CHB patients in a phase-IIa clinical trial (Yuen et al. 2014). Depth and duration of HBsAg decline and safety after a single intravenous injection of ARC-520 was assessed in 16 patients with CHB. The drug was well tolerated at the two doses given and led to significant reduction of HBsAg levels versus placebo for days 3 through 43. Another siRNA-based approach tested in chimpanzees likewise reported a favorable response (Sepp-Lorenzino et al. 2014). Extension of these studies to patients with CDH is keenly awaited.

IMMUNE THERAPEUTIC APPROACHES

Several vaccination strategies have been tested for the treatment of CHB. Trials using conventional HBV vaccines were, in general, ineffective (Lu et al. 2007; Michel and Tiollais 2010). New approaches based on DNA vaccines or anti-HBs immune complexes are being tested in clinical trials (Mancini-Bourgine et al. 2004; Xu et al. 2013; Fontaine et al. 2015). A breakthrough success would let these approaches be considered for CDH treatment.

Another immune strategy involves Toll-like receptor (TLR) ligands. TLRs are inducers of type 1 interferon responses and play a key role in the induction of the innate immune system. Several preclinical studies using different TLR ligands have been performed (for review, see Zhang and Lu 2015). A phase II clinical study of the use of the TLR 7 ligand GS-9620 is underway in CHB. Overall, immune-mediated treatment approaches will likely be optimized as an adjunct to other treatment strategies.

CONCLUSION

Pegylated interferon treatment continues to be the only effective treatment in CDH. Duration of treatment should be no less than 1 year. The surrogate marker of treatment efficacy is quantitative HDV RNA measurement. Treatment duration beyond 1 year should be decided on an individual basis, and there is need of close follow-up of patients after treatment discontinuation. Interferons are contraindicated in patients with decompensated cirrhosis, and liver transplantation must be considered in such patients. An important issue is that HDV needs to be serologically tested for in every patient with HBV and, even more so, in patients with active hepatitis B infection. New therapeutic modalities are an urgent need in this most severe form of viral hepatitis. There is now hope that alter-

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native treatment options will become available within the next 5 years.

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