REVIEW
Natural history and treatment of chronic delta hepatitis

C. Yurdaydın,1,2 R. İdilman,1 H. Bozkaya1 and A. M. Bozdayı1,2
1Gastroenterology Department, University of Ankara Medical School and 2Hepatology Institute, University of Ankara, Ankara, Turkey

Received February 2010; accepted for publication April 2010

SUMMARY. Chronic delta hepatitis (CDH) represents a severe form of chronic viral hepatitis, induced by the hepatitis delta virus (HDV) in conjunction with the hepatitis B virus (HBV). Delta hepatitis may lead to disease in humans through co-infection. The former leads to acute hepatitis which clinically can range from mild hepatitis to fulminant hepatitis and death. Severe or fulminant hepatitis is more often observed with HBV-HDV co-infection compared to HBV mono-infection. Chronic infection after acute hepatitis B + D co-infection is infrequent and similar to the rate in mono-infected patients. CDH develops in 70–90% of patients with superinfection. CDH runs a more progressive course than chronic hepatitis B and may lead to cirrhosis within 2 years in 10–15% of patients. However, as with any immune-mediated disease, different patterns of progression, ranging from mild to severe progressive disease, are observed. Active replication of both HBV and HDV may be associated with a more progressive disease pattern. Further, different HDV and HBV genotypes may contribute to various disease outcomes. CDH may be frequently associated with hepatocellular carcinoma development although recent studies provided conflicting results. The only established therapy for CDH is treatment with interferons for a duration of at least 1 year. On treatment, 6 month HDV RNA assessment may give clues as to whether to stop treatment at 1 year or continue beyond 1 year. New approaches to treatment of CDH are an urgent need of which the use of prenylation inhibitors appears the most promising.

Keywords: chronic delta hepatitis, natural history, treatment.

INTRODUCTION
Chronic delta hepatitis (CDH) represents a severe form of chronic viral hepatitis and is mostly associated with rapid progression of disease. The causative agent of CDH, the hepatitis delta virus (HDV), discovered by Rizzetto et al. in the 1970s [1], has several unique features. It is not a virus per se but can be described as a defective satellite virus that leads to hepatitis only in the presence of the hepatitis B virus (HBV). HDV has been isolated only from humans [2]. It comprises a single-stranded, circular RNA genome of close to 1700 nucleotides, which is the smallest genome of any animal virus [3]. Several features of HDV resemble those of plant viroids such as the circular configuration of its RNA genome, its RNA self-cleavage (ribozyme activity) property and its RNA to RNA rolling circle replication, but there are also important differences: (i) viroids are smaller, being 250–300 nucleotides in length; (ii) they do not require a helper virus and (iii) viroids do not code for a protein [2]. Hence, HDV is classified as a separate genus in the Deltaviridae family [4]. A further interesting characteristic of this unique agent is the recent postulate that HDV may have arisen from the human transcriptome. An in vitro human genome search for ribozymes revealed the cytoplasmic polyadenylation element-binding protein 3 (CPEB3) gene, which reportedly is structurally and biochemically related to the HDV ribozyme [5]. The CPEB3 ribozyme was found only in mammals. As CPEB3 was found not only in placental mammals but also in marsupials, it is likely that this ribozyme may have appeared at least 150 million years ago before the two groups diverged, and hence, it is postulated that HDV arose from the human transcriptome, acquiring both the delta antigen protein and the self-cleaving ribozyme from the host [5].

In recent years, several reports have suggested that with the increased control of HBV infection achieved by intense universal HBV vaccination programs, use of disposable needles, screening blood donors for HBsAg and socioeconomic improvements, HDV infection has declined significantly in many endemic areas like Southern Europe and Southeast Asia [6–9]. However, recent data suggest that this
decline may have reached a plateau, which is most likely attributable to migration and increased travel [10–13].

The current review aims to summarize recent advances in the natural history of the disease evoked by this fascinating agent and discuss its treatment. For the latter, current treatment as well as potential future treatment targets will be discussed.

**NATURAL HISTORY**

Hepatitis delta virus can be acquired either by coinfection in which an individual is confronted with both HDV and HBV viruses simultaneously, or by superinfection of individuals who are already chronically infected with HBV. HDV infection is in general associated with suppression of HBV infection as has been shown by a decline or disappearance of HBcAg in liver tissue and a decrease in HBsAg levels in early chimpanzee experiments [14].

**ACUTE DELTA HEPATITIS**

By definition, acute delta hepatitis can only be caused by coinfection of HBV with HDV where patients are confronted with both viruses. This may lead to a biphasic type of hepatitis, possibly related to sequential expression of the two viruses, which has been observed both in early chimpanzee studies [14] and prospectively in intravenous drug addicts [15]. The acute hepatitis can clinically range from mild hepatitis to fulminant hepatitis leading to death. The variable course may be a reflection of the variation in the immune response of the host or the helper function of HBV: the wider the spread of HBV to hepatocytes, the more severe the coinfection will be. In most cases, acute delta hepatitis resembles a typical self-limited hepatitis that is clinically and histologically indistinguishable from hepatitis B or other types of acute viral hepatitis. Early studies have shown that coinfection of HBV-HDV more often leads to severe or fulminant hepatitis compared to patients monoinfected with hepatitis B (Table 1). In two separate studies from Europe and the United States, the proportion of patients with evidence of delta coinfection among patients with fulminant hepatitis B and acute non-fulminant hepatitis B was 34% and 39% vs 4.2% and 19%, respectively [16,17]. In another study performed among drug addicts, patients with acute hepatitis B+D were compared to HBV monoinfected patients. Of 86 coinfected patients, 15 (17.4%) developed severe hepatitis, whereas severe hepatitis was encountered in only 2 of 50 (4%) monoinfected patients. Chronic infection developed infrequently after acute hepatitis B+D coinfection, similar to the rate in monoinfected adult patients: of 208 coinfected patients, CDH developed in 5 (2.4%) patients [18].

**CHRONIC DELTA HEPATITIS**

The chronic form of delta hepatitis (CHD) is most often the result of superinfection with HDV of a patient with chronic HBV infection, but as pointed out earlier, some infrequent cases of HBV-HDV coinfection may also evolve to chronic hepatitis. These two forms can not be differentiated on clinical or morphological grounds [19]. Superinfection with HDV may lead to clearance of both viruses in the minority of patients; in 70–90% of cases, chronic hepatitis will develop. An interesting feature of CHD mentioned in early reports is that a history of an acute hepatitis episode is frequently obtained. In an Italian cohort of 101 patients, 71 patients (70%) reported such an episode [20]. It is likely that such an episode represents the time of superinfection with HDV in a high proportion of cases. In general, CHD runs a more progressive course than chronic hepatitis B (CHB). Of 75 patients with CHD who at initial biopsy had chronic hepatitis, cirrhosis or liver failure developed in 29 patients (39%) within a follow-up of 2–6 years [20]. In a further analysis, the prevalence of histological cirrhosis showed a linear increase over the years following a reported acute hepatitis episode, reaching 23% (10/43), 41% (9/22) and 77% (9/13) after 10, 20 and 30 years, respectively [21]. However, as expected in an immune-mediated disease [22,23], CHD may run different disease courses in different individuals ranging from mildly progressive disease to a severe progressive course, which may lead to acute on chronic liver failure and death within weeks or months [24,25]. In 10–15% of patients, rapid progression to cirrhosis within 2 years has been reported [26]. The rapidly progressing form was mostly observed in intravenous drug users. This has been attributed to emergence of more pathogenic strains of HDV as a result of rapid passage of HDV from person to person in the drug community reminiscent of serial passage experiments of HDV in HBV carrier chimpanzees, which resulted in more severe hepatitis [27]. Further, active viral replication of both HBV and HDV has been reported to be associated with poor prognosis [28,29].

However, although severe disease in the acute setting of HDV superinfection is universally observed, the more progressive course of CHD after this acute setting has not been
observed everywhere. In series from the Far East, a more protracted course of CHD has been reported [30]. This may be linked to different HDV genotypes prevalent in these areas. Currently, eight genotypes of HDV have been described based on sequence variation of 19–38% [31,32]. Genotype 1 is distributed worldwide [33] with a variable disease course and genotypes 5–8 are seen in Central and West Africa. Genotype 3 has been observed in northern South American countries, such as Columbia, Venezuela, Peru and Ecuador, and is associated with a particularly severe disease [34] whereas genotypes 2 and 4, encountered in the Far East, have been associated with milder disease than genotype 1 [35,36]; a subtype of genotype 2 however has been associated with a fast progressive course [37]. The importance of HDV genotypes have been further substantiated in two recent publications, which have also pointed out the potential importance of HBV genotypes in CHD [29,38].

In a study from Brasil, HDV viral load was lower in genotype A patients compared to patients with genotype D or F HBV [38]. This difference was however not reflected in the outcome of the patients, which may have been confounded by the low number of HDV patients. In a longitudinal follow-up study of a cohort of 194 CHD patients from Taiwan with mostly genotypes B and C HBV and genotypes 1 and 2 HDV, the incidence of acute liver failure was significantly higher in genotype 1 than in genotype 2 HDV patients and on long-term follow-up genotype 1 HDV was associated with a lower remission and a higher adverse outcome rate than genotype 2. Similarly, genotype C HBV was also associated with a lower remission and a higher adverse outcome rate than genotype B. By multivariate analysis, age, genotype C HBV and genotype 1 HDV were independent factors for adverse outcome [29]. Differences in virion assembly and HDV replication may account for the variable disease course between genotype 1 and genotype 2 HDV. In vitro experiments, virion assembly efficiency has been reported to be higher with genotype 1 than with genotype 2 HDV [39]. In a cell culture assay, a genotype 2 clone of Taiwanese origin had 100-fold less RNA replication when compared with a genotype 1 clone of Italian origin [40].

More recent studies on the natural history of CHD from Italy also challenge the impression of CHD being a disease with an ominous prognosis [41,42]. It appears that CHD runs a severe course towards early development of cirrhosis in parallel with high HDV replication after which the pace of HDV replication may decrease associated with slowing of disease progression [41].

**EFFECT OF CHRONIC DELTA HEPATITIS ON ADVERSE OUTCOMES SUCH AS HEPATOCELLULAR CARCINOMA AND HEPATIC DECOMPENSATION**

Early reports suggested an infrequent association of CHD with hepatocellular carcinoma (HCC), explained by a diminished life expectancy of patients with CHD [43]. A European wide study has changed this view: it has reported a 3.2-fold increased risk of HCC development in patients with CHD compared to HBV monoinfected patients [44]. The same study also found a 2.2-fold risk of hepatic decompensation that was however not significant. In contrast, Romeo et al. [42], reported that hepatic decompensation and not HCC was the dominant complication of CHD-induced compensated cirrhosis. Two studies from Taiwan and England also failed to show an increased risk for HCC development in CHD [13,25]. Further studies on CHD-induced liver related complications are awaited for clarification.

**TREATMENT OF CHD**

The only evidence-based effective treatment of CHD consists of the use of interferon. No other medication of proven efficacy against CHD exists. The main reason behind this is that delta hepatitis-specific treatment, treatment oriented at different steps of the HDV life cycle, has not been developed. It is hoped that the first example of such an approach will be seen within one or 2 years with the use of prenylation inhibitors for the treatment of CHD in humans.

**CURRENT TREATMENT OF CHD**

The only established therapy for CDH, interferon (IFN), has to be administered for at least 1 year at high doses [45]. In the early 1990s, controlled clinical trials showed that IFN-alpha is effective in chronic hepatitis D, but relapse is high and its efficacy is related to dose and duration of therapy [45–47]. High doses (9 million units (MU) thrice weekly or 5 MU daily) for at least 1 year were required to achieve an improved outcome as determined by a biochemical and virological response [alanine aminotransferase (ALT) normalization and loss of HDV viremia measured by PCR] both of which correlate with improvement in liver histology [45,47]. Therapy with interferon is expensive and troublesome side effects are common. At the end of treatment, biochemical response may be as high as 70%, but virological response is seen in no more than 50% of patients. Despite a high rate of relapse, high dose interferon may favourably affect the natural history of the disease in the long run [47].

Long-term follow-up (median 13.0, range 2–14.8 years) of patients from the landmark study by Farci et al. [45] indicates that in patients who have received high dose INF, survival is significantly longer compared to both the low dose group and the untreated control group [48]. Seven of the 10 patients with end of treatment biochemical response, continued to have a normal ALT. However, only three patients lost HDV RNA by PCR, all of whom also lost HBsAg. It is likely that a very sensitive PCR assay had been used in this study, and the virological results may not be directly comparable to virological outcomes of other studies suggesting the importance of standardization of HDV RNA.
PCR assays. Persistent ALT normalization was also associated with significant improvement in liver histology and includes complete reversal of liver cirrhosis and fibrosis in some patients.

Some patients may need treatment beyond 1 year. This has been already shown in HBeAg-negative CHB where 2 years of IFN-alpha treatment appears to improve outcome over 1 year of therapy [49]. Common sense would suggest that patients with a partial biochemical and virological response and those who relapse after treatment discontinuation would be the typical candidates for prolonged treatment. Successful eradication of both HBV and HDV in a patient treated daily with interferon for 12 years supports this view [50]. Despite this, pilot studies of the use of INF-alpha for 2 years failed to show superiority over 1 year of therapy [51–53]. However, all of these studies were small cohort studies and did not have a comparator arm of standard 1-year treatment. Side effects decreasing compliance to treatment appears to be a problem in prolonged courses of treatment.

Experience with PEG-IFN-alpha has been reported recently by four groups [54–57]. A sustained virological response, defined as negative HDV RNA 6 months after treatment cessation was reported in 17–47% of patients. Differences in drop out rates, in the sensitivities of HDV RNA PCR assays used, in the proportion of patients who had used interferon in the past and who were cirrhotic at baseline, may account for the divergent results. Several studies emphasize the importance of measuring HDV RNA at month 6 of treatment [54,55,58]. In an analysis of baseline factors predicting response to treatment, patients who were treatment naïve at baseline or who had a low baseline GGT tended to respond better compared to patients who had used IFN in the past or whose baseline GGT was high [58]. In this study and previous studies [59], disease of short duration was predictive of response to treatment.

Nucleoside analogues (NAs) have been tested in CHD. In the past, ribavirin had been used because it had been associated with the inhibition of HDV replication in primary woodchuck hepatocyte cultures infected with HDV [60]. However, these in vitro results were not reproduced in vivo in a pilot study of nine patients with chronic hepatitis D who were given ribavirin monotherapy at a dose of 15 mg/kg daily for 16 weeks [61]. Famciclovir, lamivudine, adefovir and entecavir have also been assessed for the treatment of CHD. Unfortunately, all of them appear to be without effect in chronic hepatitis delta [57,58,62–65]. These disappointing results were to be anticipated because HDV replication does not possess a reverse transcription step [2,3]. The studies have thus confirmed the fact that CHD depends solely on HBsAg production from the helper B virus.

The best and most widely studied of the NAs is lamivudine. In the two randomized trials, lamivudine was associated with a response rate of around 10%, which may be considered as a placebo effect [63]. NAs were also without effect in terms of HDV RNA negativization in patients with HBeAg-positive CHD where higher HBV DNA levels are expected [66]. However, HBeAg-positive CHD does not represent a homogenous cohort with high HBV DNA levels; in a large European database, a quarter of HBeAg-positive CHD were actually associated with HBV DNA of <2000 IU/mL [67]. Further, HBsAg levels in HBeAg-positive CHD were higher than in HBeAg-negative CHD [67], which may account for the disappointing results of NA treatment even in HBeAg-positive CDH treated with NAs. A pilot study suggests that NAs may be beneficial in a subset of patients with high HBV DNA and very low HDV RNA [65]. Finally, another NA, clevudine, drew attention because in the woodchuck hepatitis model, it significantly inhibited the production of the surface antigen, the only HBV function on which HDV depends, in a dose-dependent manner [68], and in a preliminary study, clevudine was able to significantly decrease HDV RNA in woodchucks infected with HDV [69]. However, development of clevudine in the international market has been put on hold because of mitochondrial toxicity [70].

Several nucleoside analogues have been used in combination with interferons for the treatment of chronic hepatitis delta. Lamivudine–interferon combination treatment did not show superiority over interferon monotherapy in two randomized studies and one pilot study [58,71,72]. Both conventional and pegylated interferon have been used in combination with ribavirin [53,54,73]. In these studies, an advantage of combination treatment over IFN as monotherapy could not be shown. Finally, adefovir–pegylated IFN combination was assessed recently in the largest multicenter–multinational study so far in CHD [57]. In this study, Peg-IFN based treatment led to a 6 months post-treatment virological response rate in a quarter of patients. Although combination treatment was not more effective than peg-IFN monotherapy, combination treatment appeared to be significantly more effective compared to peg-IFN monotherapy in reducing HBsAg levels. In a subanalysis of the patient cohort from this study, quantitative HBsAg levels correlated with HDV viremia [74]. On-treatment HBsAg quantification could potentially be an important adjunct for treatment assessment [75], as is now suggested for treatment monitoring in patients with CHB treated with pegylated interferon [76].

Other substances tried for the treatment of CHD include thymic humoral factor-gamma 2 (THF-2), a synthetic thymus-derived peptide known to have a variety of immunomodulatory effects. It has been reported as being effective in chronic hepatitis B. However, no virological or biochemical effect was seen in CHD [77]. The anthelmintic drug levamisole, because of its immunomodulatory properties, was also tried but was without effect in CHD [78]. A list of drugs used so far in CHD in humans is provided in Table 2.

© 2010 Blackwell Publishing Ltd
Table 2 Medications used to treat chronic hepatitis delta in humans. Therapy with proven efficacy has been reported only for interferon alpha or pegylated interferon alpha. The others were either not effective or in the case of Combination did not provide additional benefit over interferon monotherapy.

<table>
<thead>
<tr>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon alpha</td>
</tr>
<tr>
<td>Pegylated interferon alpha</td>
</tr>
<tr>
<td>Thymic humoral factor-gamma 2</td>
</tr>
<tr>
<td>Levamisole</td>
</tr>
<tr>
<td>Ribavirin</td>
</tr>
<tr>
<td>Lamivudine</td>
</tr>
<tr>
<td>Adefovir</td>
</tr>
<tr>
<td>Entecavir</td>
</tr>
<tr>
<td>Interferon alpha + lamivudine</td>
</tr>
<tr>
<td>Pegylated Interferon alpha + ribavirin</td>
</tr>
<tr>
<td>Pegylated Interferon alpha + adefovir</td>
</tr>
</tbody>
</table>

POTENTIAL NEW TREATMENT TARGETS

Potential treatment targets can be found by investigating the life cycle of HDV. Four events can be segregated [79]: (i) attachment of the HDV virion to the hepatocyte and entrance into the hepatocyte; (ii) translocation to the nucleus; (iii) genome replication and (iv) virion assembly. Of these four steps of the HDV life cycle, two steps, the first and the last steps, are under investigation as potential treatment targets.

For the step of cellular attachment, the HBV envelope consisting of the large (L), middle (M) and small (S) surface proteins, is of importance. These proteins are all coded by a single open reading frame on the HBV genome using three different sites for initiation of translation. Recently, the hepatocyte-associated heparin sulphate proteoglycans have been identified as attachment receptors for both HBV and HDV [80,81]. Studies have highlighted the importance of the preS1 domain within the L HBsAg protein: the integrity of the N-terminal 77 amino acids in the preS1 domain and myristoylation of glycine in the preS1 domain appear to be crucial. Abolishment of HBV infection by interfering with these two properties has been shown both in vitro [80,81] and in vivo [82]. A phase I study of the use of ‘hepatocyte entry inhibitors’ is being planned in Germany.

Two approaches have been developed for potential treatment of HDV through inhibition of virion assembly and secretion. One involves the use of glucosidase inhibitors [83]. In hepatocytes infected with HBV or HDV, HBsAg leaves the hepatocyte through the endoplasmic reticulum (ER) where glucosidase enzymes of the ER modify the envelop glycoproteins so that these glycoproteins are appropriately folded for translocation through the ER. Glucosidase inhibitors by

---

**Fig. 1** Treatment algorithm suggestion for patients with chronic delta hepatitis.
causing misfolding of envelop proteins prevent secretion of virions. Although the use of glucosidase inhibitors seemed to be an attractive strategy a serious concern is the possibility that retained HBV envelop proteins may stimulate oncogenic pathways and lead to the development of HCC [84,85].

Another approach would be the use of prenylation inhibitors. The large delta antigen contains at its carboxyl terminus a cystein containing four amino acid motif serving as substrate for prenyl transferases, which add a prenyl group to the large delta antigen [86]. It has been shown that prenylation of the large delta antigen is necessary for virion morphogenesis. Prenylation inhibitors have been shown to specifically abolish HDV-like particle production in vitro [87,88] and in vivo [89], which supports its use in human delta infection because these appear to be without major side effects in humans [90].

These novel treatment strategies need testing in the human condition. For the time being however, the only management available for CHD is treatment with interferons. Based on available data mentioned in this review, we suggest the use of the algorithm outlined in Fig. 1 for the treatment of patients with CHD.

REFERENCES

1 Rizzetto M, Canese MG, Arico S et al. Immunofluorescence detection of new antigen-antibody system (delta/anti-delta) associated to hepatitis B virus in liver and in serum of HBsAg carriers. Gut 1977; 18; 997–1003.


© 2010 Blackwell Publishing Ltd
57 Wedemeyer H, Yurdaydin C, Dalekos G et al. 72 week data of the HIDIT-1 trial: multicenter randomized study comparing peginterferon-z-2a plus adefovir or peginterferon-z-2a plus placebo vs. adefovir in chronic delta hepatitis (abstr.). J Hepatol 2007; 46: 84.
8 C. Yurdaydın et al.

65 Önder FO, Yakut M, Idilman R et al. Entecavir may be beneficial in a subset of patients with chronic delta hepatitis (abstr.). Hepatology 2009; 50: 735A.
66 Yurdaydın C, Bozkaya H, Heidrich B et al. Treatment of HBcAg-positive chronic delta hepatitis with nucleos(t)ide analogs (abstr.). Hepatology 2008; 48: 722A.

© 2010 Blackwell Publishing Ltd