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Review

Treatment of chronic hepatitis due to hepatitis B and hepatitis delta virus coinfection

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ABSTRACT

An estimated 20–40 million individuals worldwide are infected with hepatitis delta virus (HDV), mostly with rapidly evolving liver disease. Therapy of chronic HDV infection remains an unmet need. To date, only interferon (IFN)-based therapy is recommended for HDV infection and response rates are unsatisfactory; in addition, many patients are intolerant to or ineligible for IFN treatment. In recent years, innovative approaches have been in development, including the following: targeting virus entry into hepatocytes; inhibition of the host enzyme farnesyltransferase by prenylation inhibitors, leading to inhibition of complete virion formation and release; blockade of hepatitis B surface antigen (HBsAg) secretion, inhibiting virus release; and IFN-lambda, which causes fewer adverse effects than IFN-alfa. Clinical trials are ongoing with encouraging preliminary results.

1. Introduction

Hepatitis delta virus (HDV) has an estimated global burden of 20–40 million chronically infected individuals; however, estimates are largely inaccurate due to the lack of systematic screening for HDV in hepatitis B surface antigen (HBsAg)-positive individuals [1,2]. Clusters of infection are still present in Eastern Europe, sub-Saharan Africa, South America and Asia [3,4]. In Western Europe, following a rapid decrease in prevalence over the period 1980–2000 [5], a re-emergence of chronic HDV infection has been noted, mostly due to immigration from endemic areas [6–9]. Eight genotypes of HDV are known [10]; genotype 1 is ubiquitous and largely predominates in Europe, whilst the other genotypes have a typical geographical distribution. Superinfection by HDV in a chronic carrier of hepatitis B virus (HBV) generates a chronic infection in >80% of cases, which may evolve rapidly towards cirrhosis and hepatocellular carcinoma; simultaneous infection by the two viruses causes severe acute hepatitis that progresses towards chronic infection in <5% of cases [11]. HBV replication is suppressed in most chronically coinfected patients; in approximately 25% HBV may dominate or both viruses may fluctuate over time [12,13].

HDV is a unique human pathogen. Its small RNA (1.7 kb) encodes for only one protein, the hepatitis delta antigen (HDAg), in two forms, namely small (S-HDAg) and large (L-HDAg), whereas it lacks functional proteins that usually drive viral replication [14,15]. As such, HDV utilises human polymerase II and to some extent polymerase I to replicate and requires HBsAg to generate the complete virion, which uses the HBV cell receptor to enter hepatocytes. Further characteristics of HDV are: (i) the presence of ribozyme, a non-coding RNA typically present in plant virusoids and some viroids, that cleaves multimeric synthesised RNA into monomeric forms; and (ii) the use of host adenosine deaminase to convert adenosine to inosine on the antigenomic RNA; this causes a change of the UAG amber codon in the S-HDAg open reading frame (ORF) to a UGG tryptophan codon for the L-HDAg ORF [16]. Finally, prenylation at the CXXX box motif (where C represents cysteine and X any other amino acid) of L-HDAg by human farnesyltransferase is critical to promote its binding to HBsAg to generate the complete HDV virion (Fig. 1).

Due to its simple structure, HDV lacks the usual targets for most antiviral drugs, e.g. viral polymerase or other functional proteins. To date, the only drug registered for HDV infection is interferon (IFN) or pegylated interferon (peg-IFN). Innovative therapeutic approaches target non-replicative steps of the virus cycle, such as entry into hepatocytes or the prenylation process. In addition, some anti-HBV drugs that block HBsAg release have the potential to prevent the production of HDV virions. This brief review focuses on the results of IFN-based therapies and examines current data on new therapies.

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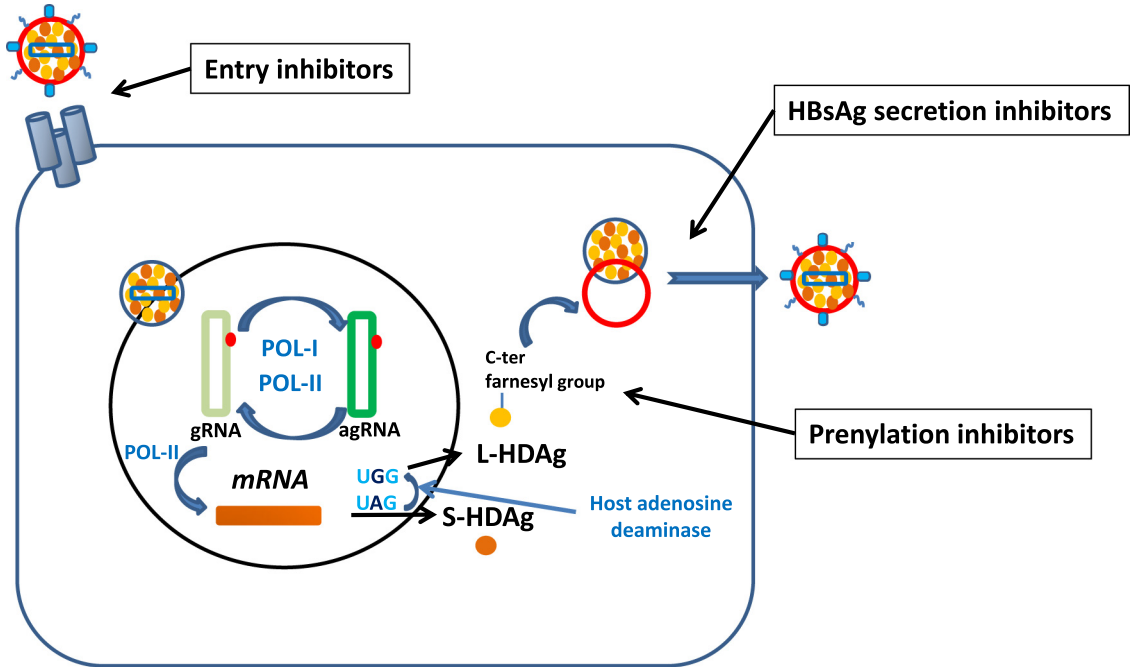

Fig. 1. Main steps in the hepatitis delta virus (HDV) replication cycle. Black arrows indicate the targets of novel therapies. agRNA, antigenomic RNA; gRNA, genomic RNA; HBsAg, hepatitis B surface antigen; L-HDAg, large hepatitis delta antigen; POL, polymerase; S-HDAg, small hepatitis delta antigen.

2. Endpoints of treatment

Antiviral treatment in chronic HDV infection, as for other chronic viral hepatitis, is aimed at preventing the progression of liver disease and death. In clinical practice and in trials evaluating antiviral drugs, surrogate efficacy endpoints are measured. The ideal endpoint is sustained undetectability of HDV-RNA in plasma, which can be achieved following HBsAg clearance; a transient presence of HDV-RNA in plasma has been reported in a few cases following HBsAg clearance [17,18]. Unfortunately, clearance of HBsAg remains a rare event with current treatments against HBV infection. In practice, a decline of HDV-RNA of ≥2 log with alanine aminotransferase normalisation at the end of therapy is considered a valuable efficacy endpoint [19]. Maintenance of response or reaching HDV-RNA undetectability at Week 24 or Week 48 after the end of therapy are additional endpoints; however, late relapses following IFN-based treatments may occur. An extensive evaluation of the endpoints of treatment in chronic HDV is available from Yurdaydin et al. [19].

In evaluating early literature studies, it must be noted that there was large variability in the sensitivity and reproducibility of HDV-RNA detection methods [20]; however, a reference standard is now available [WHO N.7657/12, Paul-Ehrlich-Institut].

3. Interferon-alfa (IFN-α)-based therapies

Recombinant IFN-α was introduced for the therapy of chronic HDV infection in the mid-1980s. It was soon clear that the standard dose of 3 million units (MU) thrice weekly had poor efficacy and that 9 MU thrice weekly or 5 MU daily were required to reach some response in terms of viral suppression. Farci et al. showed that at higher doses, IFN-α resulted in long-term improvement of liver fibrosis in some patients [21]. Another cohort study demonstrated a long-term benefit in the rate of liver-related complications and in the survival in 35 patients who responded to IFN-α given for a median of 24 months compared with those who remained viraemic [22]. In general, maintenance of viral suppression favourably influenced the clinical course of the disease, as measured by the occurrence of liver-related events, death or liver transplant. The presence of cirrhosis at baseline predicted an adverse outcome as did persistence of HDV replication or lack of IFN-based therapy [23–26]. Nevertheless, tolerability to IFN-α is poor and patients with advanced liver disease or major contraindications to IFN-α are not eligible for treatment. According to a Cochrane review, an overall a virological response was achieved in 12% of treated patients [27].

The advent of peg-IFNα simplified administration schedules but did not significantly improve treatment outcomes (Table 1) [28–40]. Two trials with peg-IFNα2b reported a sustained virological response (SVR), defined as HDV-RNA undetectable at Month 6 post-therapy, of 43% and 25%, respectively [28,29]; co-administration of ribavirin did not improve the response rate. Overall response rates obtained in studies using peg-IFNα for ≥12 months were in the range 17–47%, with the exception of one study performed in South America that reported a 95% response in patients infected by HDV genotype 3 [38]. Only three studies were randomised [29,33,36] and showed response rates from 25–31% in the treatment arms receiving peg-IFN alone for 48–96 weeks. Combination with adefovir or tenofovir was of no benefit even when treatment was prolonged to 96 weeks [33,36]. Interestingly, a 5-year post-therapy follow-up study showed that late HDV-RNA relapse, i.e. later than a SVR assessed 6 months after the end of therapy using sensitive HDV-RNA detection methods, occurred in approximately 50% of patients, suggesting that the paradigm of SVR at Month 6 post-therapy may be inappropriate for HDV [41]. These unsatisfactory results stimulated some studies aimed at identifying on therapy those patients with a higher chance of response. Niro et al. examined the kinetics of HBsAg and HDV-RNA decline and found that a decrease of both markers within Month 6 of treatment predicted the definitive clearance of HDV-RNA [42]. Keskin et al. found that patients who achieved undetectable HDV-RNA within 6 months of therapy had a high probability of maintaining virological response at Week 24 after the end of therapy [43]. Lutterkort et al. found that a pre-therapy virological pattern of dominance of HBV replication (found in 7% of 109 patients) or of non-dominance (in 17%; i.e. the viral load of one virus did not exceed that of the

Table 1
Summary of studies using pegylated interferon (peg-IFN) for chronic hepatitis delta virus (HDV) infection.

References	Type/dose	No. of patients	Duration of therapy	Duration of follow-up	Overall virological response at EOT (%)	SVR (%)
[28]	Peg-IFNα2b 1.5 μg/kg	14	12 months	16 months	57	43
[29]	Peg-IFNα2b 1.5 μg/kg	16	18 months	6 months	19	25
	Peg-IFNα2b 1.5 μg/kg + RBV	22	12 months	6 months	9	18
[30]	Peg-IFNα2b 1.5 μg/kg	12	12 months	12 months	–	17
[31]	Peg-IFNα2b 1.5 μg/kg	49	13 months	26 months	33	25
[32]	Peg-IFNα2b 1.5 μg/kg	11	24 months	6 months	56	–
		7	12 months	6 months	57	
[33]	Peg-IFNα2a 180 μg	29	12 months	6 months	24	31
	Peg-IFNα2a 180 μg + adefovir 10 mg/day	31	12 months	6 months	23	24
	Adefovir 10 mg/day	30	12 months	6 months	0	0
[34]	Peg-IFNα2b	277 enrolled (238 evaluated)	48 weeks	24 weeks	29.8	29.4
[35]	Peg-IFNα2a 180 μg or peg-IFNα2b 1.5 μg/kg	32	24 months	6 months	50	47
[36]	Peg-IFNα2a + tenofovir	59	96 weeks	24 weeks	48	29
	Peg-IFNα2a + placebo	61	96 weeks	24 weeks	33	21
[37]	Peg-IFNα2a 90–270 μg/week	13	6–240 weeks (median, 140 weeks)	–	–	39 (3 lost HBsAg)
[38] [a]	Peg-IFNα2a 180 μg + entecavir 0.5 mg/day	22	48 weeks	48 weeks	95	95
[39]	Peg-IFNα2a	41	12 months		39	37
	Peg-IFNα2b	15	12 months		13	13
[40]	IFN or peg-IFN	99	6–126 months (median, 24 months)	24–225 months (median, 55 months)	–	35.3

EOT, end of treatment; SVR, sustained virological response; RBV, ribavirin; HBsAg, hepatitis B surface antigen.
[a] South American study enrolling patients with HDV genotype 3.

other virus) was associated with a favourable cytokine/chemokine network and a higher response rate to peg-IFNα compared with patients with HDV dominance [44]. It remains unclear whether therapy should be prolonged on the basis of individual kinetics of HBsAg decrease in patients who achieve negative HDV-RNA. The recently introduced HBV marker, hepatitis B core-related antigen (HBcrAg), might have a role in defining the progression of liver disease in combination with other virological markers [45] but has not been assessed as a predictor of response to therapy.

4. Nucleos(t)ide analogues

Lamivudine, administered alone or in combination with IFN, was ineffective in inducing a decrease in HDV-RNA [46–48]. The same results were obtained with adefovir [33]. Current-generation analogues (entecavir, tenofovir) given alone for 24–96 weeks were also ineffective. In a well-designed randomised trial, tenofovir plus peg-IFNα for 96 weeks resulted in a better virological response at the end of treatment compared with peg-IFNα alone; however, the advantage was lost during the post-therapy follow-up [36,49,50]. In patients with advanced liver disease replicating both HBV and HDV and treated with entecavir or tenofovir for a median of 50 months, liver-related event rates were 3–10-fold higher than in pair-matched HBV monoinfected patients receiving the same therapy [51]. In all, therapeutic attempts to decrease the background of HBV infection failed to decrease HDV production since analogues did not affect HBsAg production.

5. Entry inhibitors

HBV enters hepatocytes through binding of the pre-S1 domain (S-HBsAg) of HBsAg with its receptor on the hepatocyte membrane, the sodium-taurocholate cotransporter peptide (NTCP), which drives the internalisation process [52]. HDV, being coated with HBsAg, utilises the same receptor (Fig. 1). Myrcludex B (MyrB; bulevirtide) is a synthetic *N*-acylated peptide derived from the pre-S1 domain that inhibits the HBV receptor on the hepatocyte surface and prevents the infection of healthy cells and viral spread within the liver [53]. Other classes of entry inhibitors, not targeting NTCP, have been tested in vitro. Bogolomov et al. provided the proof of concept that MyrB could decrease HDV viraemia [54]. They randomised 24 patients to three groups that received, respectively: MyrB 2 mg daily as subcutaneous (s.c.) injection for 24 weeks, followed by weekly peg-IFNα2a alone for 48 weeks (Myr cohort); MyrB 2 mg daily plus peg-IFNα2a for 24 weeks, followed by peg-IFNα2a alone for 24 weeks (Myr-IFN cohort); and peg-IFNα2a alone for 48 weeks (IFN cohort). At an interim analysis at Week 24 of treatment, they demonstrated a decline of ≥1 log in HDV-RNA in 6/7 evaluable patients in the Myr group, with disappearance in 2; in 7/7 patients in the Myr-IFN group, with disappearance in 5; and in 6/7 patients treated with peg-IFNα2a alone. In a phase 2 study, 120 patients, all receiving tenofovir for ≥12 weeks, were assigned to add 2, 5 or 10 mg of MyrB subcutaneously for 24 weeks or no MyrB [55]. An HDV-RNA decline of ≥2 log was achieved at Week 24 in 46.4% of the 2 mg group, 46.8% of the 5 mg group and 76.6% of the 10 mg group [55]. This was an interesting proof of concept that IFN-free therapy is feasible in chronic HDV infection; surprisingly, no patient achieved the primary endpoint of an HBsAg decline of ≥0.5 log IU/mL. MyrB was generally safe; it caused an elevation in the concentration of serum bile acids in all dosed patients that remained clinically silent and promptly returned to normal after the end of therapy. Phase 3 studies are in progress exploring longer treatment durations or various combinations with peg-IFN. Recently, the safety and efficacy of MyrB monotherapy at a daily dose of 10 mg for 48 weeks was reported in three patients with cirrhosis treated on a compassionate basis [56].

6. Prenylation inhibitors

These drugs target the host enzyme farnesyltransferase, which catalyses the farnesylation process at the carboxy edge of L-HDAg, thus making it able to bind HBsAg. Lonafarnib (LNF) was first introduced as an anti-leukaemia drug. Its use in chronic HDV infection

was first assessed in vitro and in vivo in a mouse model [57,58]. In a phase 2A, randomised, proof-of-concept study, Koh et al. assigned 14 HDV patients to receive oral LNF at 100 mg (group 1) or 200 mg (group 2) twice a day or placebo for 28 days, followed by a 6-month follow-up; the primary outcome was a decrease in serum HDV-RNA [59]. By the end of therapy, the mean HDV-RNA decline in serum from baseline was 0.73 log IU/mL [95% confidence interval (CI) 0.17–1.31] in group 1 and 1.54 log IU/mL (95% CI 1.21–1.93) in group 2 versus 0.13 log IU/mL (95% CI –0.14 to 0.37) in the placebo group. At post-therapy follow-up, HDV-RNA returned to baseline in all patients. Gastrointestinal symptoms, including nausea and diarrhoea, were common in patients receiving LNF. Interestingly, the dose-dependent effect of LNF was further demonstrated by the linear correlation between serum concentration of the drug and HDV-RNA decline. To increase concentrations of LNF and to overcome its toxicity, the combination of ritonavir (RTV), a CYP3A4 inhibitor, with 100 mg LNF was proposed. In a proof-of-concept study, Yurdaydin et al. showed that the RTV/LNF combination, administered twice daily, had better antiviral activity than LNF 300 mg twice daily with less adverse events [60]. In addition, in the same study a synergistic effect of the combination of LNF + peg-IFNα was shown, thus supporting further development of the drug. A multicentre phase 3 trial is now ongoing.

7. Blockade of hepatitis B surface antigen release/production

Nucleic acid polymers (NAPs) inhibit the release of HBV subviral particles; since HDV virions use the same secretion mechanism, a therapeutic effect on HDV infection was hypothesised. In vitro, these compounds blocked HDV infection in cultures of differentiated human hepatoma cells [61]. In a chronic duck HBV infection model in Pekin ducks, synergy with nucleos(t)ide analogues was noted [62].

Bazinet et al. treated 12 non-cirrhotic patients with chronic HDV infection (>6 months) with 500 mg of intravenous REP 2139 weekly for 15 weeks, followed by combined therapy with 250 mg of intravenous REP 2139 and 180 μg of s.c. peg-IFNα2a weekly for 15 weeks, and then monotherapy with 180 μg of peg-IFN weekly for an additional 33 weeks [63]. All patients were followed-up for 1 year after the end of therapy. Six patients achieved an HBsAg level <0.05 IU/mL; the suppression was maintained at the end of follow-up and all patients developed significant hepatitis B surface antibody (anti-HBs) titres. Eleven patients became HDV-RNA negative during treatment, with seven of them remaining negative by the end of follow-up. Hair loss, dysphagia and dysgeusia have been reported with NAPs. Elevation of serum aminotransferases was recorded in all patients with HBsAg suppression at <1 IU/mL. This latter event was also observed in patients with HBV monoinfection receiving NAP with peg-IFN and tenofovir and may limit the use of this treatment in patients with cirrhosis. The mechanism of inhibition of HDV replication by NAPs is not fully clarified, although accumulation of HDV L-protein inside hepatocytes could play a role.

8. Interferon-lambda (IFN-λ)

IFN-λ could be an alternative to IFN-α since it binds the type 1 IFN receptor that is prevalently expressed on hepatocytes; as a consequence, less systemic adverse effects are expected. In HBV/HDV-infected humanised mice, both IFN-α and IFN-λ reduced intrahepatic HDV infection markers [64]. In a phase 2 study, 33 patients with chronic HDV infection were randomised to receive peg-IFNλ at a dose of either 120 μg or 180 μg by weekly s.c. injection for 48 weeks; all patients also received daily tenofovir or entecavir [65]. A 2 log decrease in HDV-RNA was achieved in 53% and 90% patients, respectively. Typical adverse effects seen with IFN-α were fewer, but 10% of patients experienced hyperbilirubinemia and/or alanine aminotransferase increase; both effects were reversed by dose reduction. A phase 2a open-label study to evaluate the safety and antiviral effects of triple therapy with LNF/RTV and IFN-λ for a period of 24 weeks is ongoing.

9. Conclusions

For decades, treatment for chronic HDV infection has been based on IFN-α, leading to unsatisfactory results. New therapeutic approaches provide some hope for the near future, since efficacy results surpassed those achieved with IFN and tolerability looked better than for IFN. Controlled trials are ongoing and will quantify the advantages. However, most studies still combine the new agents with peg-IFN, which involves the limitations of this treatment. IFN-λ could be an alternative since it causes fewer adverse events than IFN-α. Theoretically, IFN-free combinations of two drugs with or without a nucleot(s)ide analogue could be an interesting option, which requires further investigation

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