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Recent breakthroughs in the treatment of chronic hepatitis Delta

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SUMMARY

Hepatitis Delta virus (HDV) is responsible for the most aggressive form of chronic hepatitis, which may evolve towards cirrhosis, hepatocellular carcinoma and death within few years. During the last 30 years the only available therapy was interferon or peg-IFN, which was characterized by poor tolerability and modest results. The detailed knowledge of the HDV replication cycle and its interaction with HBV allowed the introduction of new drugs which are currently in phase II or III of experimentation. Basically, bulevirtide, to date the only one approved by EMA, inhibits the entry of the virus into the hepatocytes and hence its intrahepatic spread; lonafarnib inhibits the pharnesylation process of the L-HDAg, which is critical for the assembly of the HDV virion; the nucleic acid polymers (NAPs) mainly block the production/release of HBsAg. The available clinical trials with these compounds showed an excellent anti-viral activity against HDV.

Keywords: hepatitis D, peg-IFN, bulevirtide, lonafarnib; NAP.

INTRODUCTION

Chronic infection with hepatitis Delta virus (HDV) is estimated to affect around 20 millions of HBsAg positive individuals worldwide; however, the lack of systematic screening for hepatitis Delta in HBsAg positive individuals makes the estimate inaccurate. Hyper-endemic areas are still present in East Europe, sub-Saharan Africa, Middle East (Iran), South America and Asia (Mongolia, Vietnam); recently, a spread of HDV infection was noted among injection drug users in San Francisco. In Western Europe the prevalence of the infection declined over the years 1980-2000, then a re-emergence was noted due to the immigration from endemic countries [1-5].

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HDV causes the most aggressive form of chronic hepatitis, which may evolve towards decompensated cirrhosis and hepatocellular carcinoma in few years. It infects humans as coinfection (simultaneous infection by HBV and HDV) or superinfection (HDV infection in HBsAg positive subjects). The latter modality generates a chronic infection in 80% of the cases [6].
From its discovery in the year 1977 the biology of the virus has been elucidated by numerous studies; however, the therapy of the infection remained for decades an unmet need [7]. This review focuses on the recent progresses in the therapy of chronic hepatitis Delta.

Replication cycle

HDV needs the HBV surface antigen (HBsAg) to generate the complete virion. The HBsAg coat permits the Delta virus to enter the hepatocytes: it is captured by heparan sulphate proteoglycans (HSPG) present on the cell membrane and inter-

nalized through the Na-taurocholate cotransport protein (NTCP) which is the HBV specific receptor (Figure 1). Then, HDV is uncoated into the cytoplasm of the hepatocytes and its genome transported into the nucleus; HBV has no role in the subsequent replication steps. HDV small circular RNA genome (1.7 Kb) encodes for only one protein, the Delta antigen (HDAg), in the two forms small (S-HDAg) and large (L-HDAg), which contains an extra 19 amino acids, both assembled in a nucleocapsid-like ribonucleoprotein (RNP). The genome lacks the functional proteins that usually drive viral replication [7, 8]; as such, HDV utilizes human polymerase II and to some extent polymerase I to replicate. Further characteristics of HDV replication cycle are:

a) the presence of ribozyme, a non-coding RNA typically present in plant virusoids and some viroids, which cleaves multimeric synthesized RNA into monomeric forms;
b) the use of host adenosine deaminase to convert adenosine to inosine on the antigenomic RNA; this causes the change of the C-terminal UAG amber codon in S-HDAg ORF to UGG tryptophan codon in L-HDAg ORF; this change is critical to allow the following step;
c) prenylation at the CXXX box motif (where C represents cysteine and X any other aminoacid) of the large delta antigen by the human farnesyltransferase, which promotes its binding to HBsAg to generate the complete HDV virion (Figure 1). Eight genotypes of HDV are known with high sequence variability; genotype 1 is ubiquitous and largely predominates in Europe [9].

Endpoints of therapy

The endpoint of antiviral therapies is stopping the progression of the liver disease and possibly causing its regression. In clinical settings we need validated surrogate markers [10]. The best endpoint of therapy is HBsAg loss; unfortunately, this target is hard to reach at present. Clinical trials and clinical practice adopt HDV RNA negativity, maintained at least six months after the end of therapy (EoT). Beside this, recent trials used as endpoint the reduction of HDV RNA of at least 2 $\log_{10}$ from baseline; the clinical significance of this partial achievement is questionable. Liver histology allows the detection of HD antigen in the nuclei of the hepatocytes by immunofluorescence; it correlates with viral load. Finally, about 50% of the patients who were HDV RNA negative at the week 24 after stopping Peg-IFN therapy relapsed during a follow-up period of 5 years [11]. Thus, the paradigm of the sustained virological response assessed at week 24 after EoT does not apply to hepatitis Delta.

Therapy

For years, the only drug recommended against HDV remained IFN or pegylated interferon (peg-IFN). Innovative therapeutic approaches target non-replicative steps of virus cycle, or also the production/release of HBsAg. The characteristics of the drugs against HDV are summarized in Table 1.

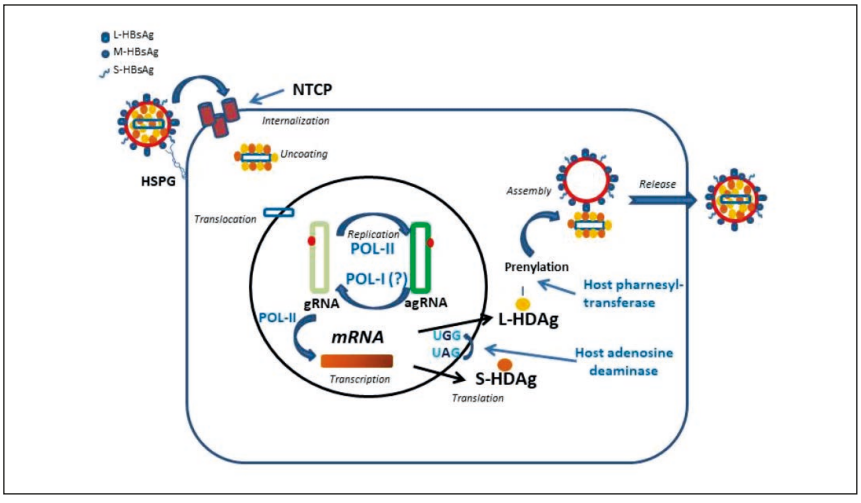

Figure 1 - Main steps of the HDV life cycle. HSPG = heparan sulphate proteoglycans; NTCP = Na-taurocholate cotransport protein.

Interferons alfa

Recombinant interferon (rIFN) alfa and then Peg-IFN alfa were for decades recommended for hepatitis Delta, although never formally approved by drug regulatory Agencies. In the early 1990's three studies assessed the superiority of rIFN versus no treatment in inducing clearance of HDV-RNA at the end of treatment, all recording a high rate of relapses in the post treatment period [12-14]. Importantly, the studies demonstrated that the patients who maintained HDV-RNA negativity showed a histological and clinical improvement; in addition, the higher doses of rIFN and a duration of treatment of at least 12 months were associated to better results. These concepts were confirmed after peg-IFN was introduced [15].

There is a lack of randomized trials comparing peg-IFN treatment versus placebo or rIFN. A randomized study compared peg-IFN alfa given at the standard weekly dose of 180 µg s.c. versus adefovir given alone or the combination of the two drugs, given for 48 weeks [16]. At week 24 post-EoT 28% of the patients in the groups receiving peg-IFN were HDV-RNA negative versus 0% in the group receiving adefovir alone. In a further randomized trial Peg-IFN at standard dose was given for 96 weeks and compared to Peg-IFN plus tenofovir disoproxil fumarate at 300 mg/day, orally [17]. At week 24 post EoT a relapse was noted in 40% of the patients who were HDV-RNA negative at EoT, so finally HDV-RNA negative patients were 31% vs 23%, respectively (ns). Thus, adding a nucleotide analogue to peg-IFN was of no benefit. The combination of peg-IFN with ribavirin was tested in a randomized trial with negative results [18].

Various patient series using Peg-IFN alfa showed response rates between 17 and 47%, usually assessed at week 24 post-EoT [reviewed in ref. 19]. A major limit is that the patient populations among the studies were heterogeneous as for age and prevalence of cirrhosis; in addition, treatment duration and criteria for response were various and the methods used to measure HDV-RNA in serum were not standardized. These variables make it hard to compare the results. In general, the tolerability of peg-IFN was poor; in patients with compensated cirrhosis and no portal hypertension it should be administered by a trained specialist whereas the presence of portal hypertension or decompensated cirrhosis is an absolute contraindication.

Nucleo(s)tide analogues (NAs)

NAs had no effect on HDV viremia; long term treatment did not affect clinical outcome substantially [20]. However, NAs are recommended in the presence of ongoing or fluctuating HBV-DNA in serum at >2,000 IU/mL with the aim of avoiding ALT flares due to HBV replication, which could precipitate the progression of the liver damage;

Table 1 - Main characteristics of the drugs active against hepatitis delta virus.

Active drugs	*Administration route*	*Mechanism of action*	*Side effects*	*Duration of treatment*
Peg-IFN alfa	Subcutaneous weekly	Immunomodulator Induces IFN-stimulated genes	Flu-like syndrome Fatigue Depression Reduction in WBC and Plt count	48 weeks
Peg-IFN lambda	Subcutaneous weekly	Immunomodulator Induces IFN-stimulated genes	As for Peg IFN alfa, but milder Hyperbilirubinemia	48 weeks
Bulevirtide	Subcutaneous daily	Entry inhibitor	Asymptomatic increase in bile acid level in the blood	24-48 weeks Maintenance therapy and combination with Peg-IFN under study
Lonafarnib + ritonavir	Oral daily	Prenylation inhibitor	Mild gastrointestinal	24-48 weeks
Nucleic acid polymers (NAPs)	Intravenous weekly	HBsAg release inhibitor; assembly inhibitor	Transient ALT elevation	24-48 weeks

NAs treatment is mandatory in patients with advanced liver disease [21].

Peg-Interferon lambda

IFN lambda has been considered an alternative to IFN alfa, since it binds Type 1 IFN receptor which is prevalently expressed on the hepatocytes; as a consequence, less systemic adverse effects are expected. In a phase 2 study, 33 patients with chronic hepatitis Delta were randomized to receive peg-IFN Lambda at the dose of either 120 or 180 µg, by weekly subcutaneous injections, for 48 weeks; all patients received daily tenofovir or entecavir [22]. A 2 log^{10} decrease in HDV-RNA was achieved in 53% and 90% patients, respectively. Typical adverse effects seen with IFN alpha were fewer with peg-IFN lambda, but 10% of the patients experienced hyperbilirubinemia and/or ALT increase; both effects were reversed by dose reduction. A phase 2a open label study is ongoing, to evaluate the safety and antiviral effects of triple therapy with lonafarnib/ritonavir and IFN-lambda for a period of 24 weeks [23].

Entry inhibitor

Bulevirtude (Hepcludex®; previously Myrcludex-B) is a synthetic N-acylated peptide derived from the pre-S1 domain of HBV, which binds to HBV receptor NTCP on the hepatocyte surface and prevents the infection of healthy cells and viral spreading within the liver [24]. Hepcludex® obtained the conditional approval by EMA in July 2020 as 2 mg vials to be administered sc daily.

Bogolomov et al. provided the proof of concept that BLV could decrease HDV viremia [25]. They randomized 24 patients in three groups that received, respectively: BLV 2 mg daily as sc injection for 24 weeks, followed by weekly Peg-IFNα2a alone for 48 weeks (Myr cohort); BLV 2 mg daily plus Peg-IFNα2a for 24 weeks, followed by Peg-IFNα2a alone for 24 weeks (Myr-IFN cohort); Peg-IFNα2a alone for 48 weeks was administered in the third group (IFN cohort). At week 24 of treatment they demonstrated a decline ≥1 log in HDV-RNA in 6 out 7 evaluable patients in Myr group with negativity in 2; in 7/7 patients receiving combination, with disappearance in 5, and in 6/7 patients treated with Peg-IFNα2a alone. Following this study, a phase II dose-finding, randomized trial (Myr 202) enrolled 120 patients in four arms receiving, respectively, daily BLV 2, 5 or 10 mg sc, with daily tenofovir, for 24 weeks; a fourth arm received tenofovir alone [26]. At the EoT the virological response (≥2 log_{10} HDV-RNA decline) was obtained in 46.4, 46.8, 76.9 and 3.3%, respectively, in the four arms. Surprisingly, no patient achieved the primary endpoint of an HBsAg decline of at least 0.5 log IU/mL Importantly, the combination of daily BLV 2 or 5 mg with weekly Peg-IFN for 48 weeks was proved synergistic in the Myr 203 trial [27].

The Myr 204 study is a phase 2b trial which randomized HDV patients to receive for 48 weeks a) 2 or 10 mg BLV sc daily plus weekly peg-IFN alfa 180 ug, (50 pts for each BLV dose); 2) Peg-IFN alfa alone (24 pts); 3) BLV alone 10 mg sc daily (50 pts); at an interim analysis on week 24 of therapy [28] the endpoint of a HDV-RNA decline of at least 2 log_{10} was achieved in 38% of those receiving peg-IFN alone; 72% in the BLV 10 mg arm; 88% and 92%, respectively, in patients treated with 2 or 10mg BLV plus peg-IFN. The ongoing phase 3 trial (Myr 301) randomized 150 patients to explore long-term treatment (96 or 144 weeks) with either BLV 2 or 10 mg; an interim analysis at week 24 of treatment showed virological response (≥2 log_{10} decline) in 55.1% and 68%, respectively, in patients being treated with BLV 2 or 10 mg [29].

In all studies, BLV was generally safe; it caused an elevation in the concentration of serum bile acids in all dosed patients, that remained clinically silent (no case of itching recorded) and promptly returned to normal after the end of therapy. Recently, one case of hypersensitivity reaction was reported [30].

In addition to randomized trials, at least two observational cohorts provided interesting data. The French ATU study treated 145 patients on compassionate basis, with either 2 mg BLV daily in monotherapy (n=77) or plus Peg-IFN alfa weekly (n=68). At month 12 of therapy, 68.3% in the mono-group and 93.9% in the combination group reached the endpoint (≥2 log_{10} HDV-RNA decline) [31]. Loglio et al. reported 3 patients with cirrhosis and portal hypertension who received BLV for three years, with excellent virological, biochemical and clinical response and no adverse events [32].

In conclusion, BLV is a highly promising drug. However, the optimal duration of treatment is unknown and the need for a maintenance therapy need to be explored. At present, most of the

studies quoted above have been presented at International Meetings and published in abstract form; we are waiting for more details and the proportions of patients who maintain undetectable HDV-RNA off-therapy.

Prenylation inhibitor

The host enzyme farnesyltransferase, which catalyses the prenylation process at the carboxy edge of L-HBsAg, is the target Lonafarnib (LNF) was introduced as an anti-leukemia drug and then approved for progeria syndrome. Its use in chronic HDV infection was first assessed *in vitro* and *in vivo* in a mouse model, since it inhibits the host enzyme farnesyltransferase which is essential in promoting virus packaging (Figure 1) [33, 34]. In a phase 2A randomized, proof-of-concept study, Koh et al. assigned 14 HDV patients to receive oral LNF at 100 (group 1) or 200 mg (group 2) orally twice a day or placebo for 28 days, followed by six month follow-up; the primary outcome was a decrease in serum HDV-RNA [35]. By the end of therapy, the mean HDV RNA decline in serum from baseline was 0.73 log (0.17-1.31) in group 1, and 1.54 log (1.21-1.93) in group 2 vs. 0.13 log in the placebo group. On post-therapy follow-up HDV-RNA returned to baseline in all patients. Gastrointestinal symptoms, including nausea and diarrhoea, were common in patients receiving lonafarnib. To increase concentrations of LNF and overcome its toxicity, the combination of 100 mg ritonavir (RTV), a CYP3A4 inhibitor, with 25 to 100 mg LNF was introduced. In a proof-of-concept study, Yourdaydin et al. showed that ritonavir/LNF bid had better antiviral activity than LNF 300 mg bid, with less adverse events [36]. In addition, in the same study a synergetic effect of the combination of LNF plus Peg-IFN alfa2a was shown, thus supporting further development of the drug. A multicenter phase 3 trial is now ongoing which randomizes 400 patients in four arms to receive, respectively, LNF 50 mg/RTV 100 mg bid, LNF 50 mg/RTV 100 mg bid plus weekly pegIFN alfa 180 µg, pegIFN alfa alone, placebo, all for 48 weeks.

Inhibitors of HBsAg synthesis/release

As recalled above, the loss of HBsAg can stop the production of new HDV virion. Nucleic acid polymers (NAPs) inhibit the release of HBV subviral particles. These compounds blocked HDV infection in cultures of differentiated human hepatoma cells and in the model of Pekin duck; a synergy with nucleos(t)ide analogues was noted [37]. Bazinet et al. treated 12 non-cirrhotic patients with chronic HDV infection with REP 2139 500 mg given i.v. weekly for 15 weeks followed by weekly 250 mg REP 2139 plus Peg-IFN alfa2a 180 mg sc for 15 weeks and then Peg-IFN alone for additional 33 weeks [38]. Six patients achieved an HBsAg level <0.05 IU/mL; the suppression was maintained at the end of one year follow-up in 5 and all developed significant anti-HBs titres; eleven patients became HDV-RNA negative during treatment, 7 of them remaining negative by the end of follow-up. An asymptomatic ALT elevation was common during treatment; hair loss, dysphagia, and dysgeusia were also reported. An extended follow-up to 3.5 years confirmed HDV response in 7 patients [39]. Interestingly, no major safety issues emerged; a transient aminotransferase elevation was recorded in some patients who attained HBsAg loss in the post-therapy period.

Other promising agents are in clinical trial pipeline with the primary aim of obtaining HBV functional cure. These include si-RNAs, anti-sense oligonucleotides (ASOs), checkpoint inhibitors, immunostimulators. However, their efficacy against HDV remains to be established.

Liver transplant

Due to currently limited treatment options for HDV infection, many patients with HDV progress to cirrhosis and its complications, including the development of hepatocellular carcinoma.

Liver transplant (LT) remains the only option for patients with HDV end-stage liver disease, HCC or fulminant liver failure. An Italian study found that HDV co-infected patients were about one third of HBsAg positive patients undergoing LT [40].

Interestingly, several studies have shown that the presence of HDV infection appears to provide a protective effect against HBV reinfection in LT patients, possibly via suppression of HBV replication resulting in longer survival rates [41, 42]. Recently a study published on LT patients in Brazil, where HDV genotype 3 prevails, showed significantly higher 4-year survival rate of 95% in HDV group (n=29), compared to 75% in HBV group (n=40) [43]. On the other hand, the risk of post-LT HCC recurrence doesn't differ between HBV and HBV-HDV patients.

According to the international guidelines, us-

ing HBIG in conjunction with oral antivirals post-transplantation is the treatment of choice after LT to prevent HBV-HDV recurrence [44].
Since HDV coinfection worsens the prognosis of HBV patients with end-stage liver disease and, simultaneously, post-LT outcome is better (no worse in any case) in HDV coinfected patients, we can conclude that HDV patients are optimal candidates to LT because they have an intrinsic high transplant benefit (*i.e.* the difference between post LT survival and survival without LT).

CONCLUSIONS

Hepatitis Delta remained a neglected disease in the last decades mainly due to the lack of an effective and largely applicable antiviral treatment. As a consequence, the attitude for HDV testing declined over time and the global burden of the disease is likely to be underestimated. The availability of the new drugs could be a potent incentive to identifying HDV patients who may benefit from the therapy.
However, the way towards a universal therapy for HDV patients is still long. Indeed, there is uncertainty about the optimal length of the treatment, the off-treatment results, the need for a maintenance therapy. The therapy with bulevirtide or lonafarnib obtained the best results in combination with peg-IFN; as such, many patients are not eligible due to intolerance or contraindication to peg-IFN. Moreover, neither drugs in monotherapy has been tested in decompensated cirrhosis, for which liver transplant remains the sole option. Nevertheless, the perspective is optimistic, since the above-mentioned therapies have the potential to reduce the disease burden and other promising treatments – as the novel antivirals against HBV - are on the way.

Conflict of interest
The authors declare no potential conflicts of interest.

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