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Beyond Pegylated Interferon-Alpha: New Treatments for Hepatitis Delta

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Abstract

Persistent coinfection with the hepatitis B/D viruses (HDV) represents the most severe form of viral hepatitis. Hepatitis D often leads to liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma. The current treatment options are limited as only pegylated interferon-alpha (PEG-IFNα) has efficacy against HDV. However, treatment response is still unsatisfactory with 25-40% HDV RNA suppression after 1-2 years. In addition, late HDV RNA relapses have been described during long-term follow-up. Fortunately, new treatment options for patients with chronic hepatitis delta are now on the horizon. The hepatocyte entry inhibitor bulevirtide (formerly myrcludex B) and the farnesyl transferase inhibitor lonafarnib are currently explored in patients with chronic hepatitis delta in Phase 3 clinical studies. The nucleic acid inhibitor REP-2139-Ca and PEG-IFN-lambda are studied in Phase 2 trials. We here summarize data on the efficacy of these new antiviral drugs and the existing safety data on the treatment of HDV infection. **(AIDS Rev. 2019;21:126-134)**

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Key words

Hepatitis B virus/hepatitis D (delta) virus coinfection. Myrcludex B. Bulevirtide. Lonafarnib. REP-2139-Ca. Pegylated interferon-lambda.

Introduction

Coinfection with hepatitis B virus (HBV) and hepatitis D (delta) virus (HDV) represents the most severe form of viral hepatitis with an estimated more than 10-25 million coinfected people worldwide[1]. A recent meta-analysis suggested an even higher HDV prevalence with up to 1% of the world population being possibly HDV infected[2]. This analysis has been criticized as many studies included in this meta-analysis were biased by referral effects or disease severity[3,4]. Thus, reliable data on the global HDV prevalence are still lacking. However, it is quite clear that the HDV prevalence is higher in distinct risk groups including HIV-infected individuals. Very early studies published in the 1980s and 1990s suggested already that HDV infection often leads to liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma[5,6] which has been confirmed in more recent single-center examinations published during the past

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10 years[7-12]. In studies from HIV-HBV-HDV-coinfected patients, HDV replication was determined as an independent factor associated not only with hepatic complications but also even with an increased overall mortality[13,14]. Eight different genotypes have been described with different geographical distributions[15,16]. Determination of HDV genotypes and the global distribution of these genotypes may be important as they could affect disease prognosis and treatment outcome[17]. HDV genotype 1 has a worldwide distribution, whereas genotypes 2 and 4 are mainly seen in the Far East, genotype 3 in Northern South America, and genotypes 5-8 have only been described in Africa[18]. HDV genotype 3 has been associated with a particular severe course of hepatitis with many patients developing clinical complications during the first 10-20 years of infection at relatively early ages[19].

So far, the only antiviral treatment with proven efficacy against HDV is based on administration of type 1 interferons (IFNs), in clinical practice pegylated IFNα (PEG-IFNα). Treatment response is observed in around 25%-40% after 1 year of treatment[20,21] and extending treatment period to 96 weeks and adding tenofovir disoproxil fumarate resulted in no significant improvement in HDV RNA response rates at the end of treatment[22]. Antiviral treatment with PEG-IFNα can be associated with frequent and sometime severe side effects and cannot be administered in patients with advanced liver cirrhosis. Therefore, there is an urgent need for new treatment options in hepatitis delta patients.

Goals of antiviral treatment of hepatitis delta

The ideal endpoint of any antiviral therapy of hepatitis delta is not only clearance of HDV but also the loss of HBsAg which would mean functional cure of hepatitis B[23]. If HBV infection is cured, transmission of HDV is also prevented. Loss of HBsAg induced by antiviral treatment has been associated with improved clinical outcomes[11,24,25]. If HBsAg remains detectable, there is evidence that HDV RNA suppression is associated with an improved clinical long-term outcome. Lower HDV RNA levels have been associated with a reduced risk for progression to liver cirrhosis[26,27]. Recent single-center studies confirmed that a virological response, for example, undetectable HDV RNA, to IFN-based treatment could be linked to a better clinical outcome[11,12]. Patients who develop a late HDV RNA relapse after initial responses did not develop hepatic events during 5 years of follow-up[28]. Still, there is a matter of debate which viral surrogates can be used also for clinical trials as endpoints that reliably could indicate a better or worse clinical course of the infection[18]. It has been suggested that viral efficacy of a drug should lead to an HDV RNA decline of at least 2 log and that a biochemical improvement as defined by normalization of ALT levels should be achieved (Table 1).

IFNα

Since the 1980s, IFNα has been used to treat hepatitis delta. There is a large variation of HDV RNA decline and suppression between different studies (0-40%) as therapies were administered in diverse protocols and designs[29]. In the two largest randomized controlled trials, IFNs led to a post-treatment week 24 viral response (undetectable HDV RNA) in 25%-30% of patients[21,22]. PEG-IFNα must be administered as subcutaneous injections and can be associated with a variety of side effects possibly affecting many organs and parameters. Importantly, a large proportion of HDV-infected patients cannot be treated with PEG-IFNα due to contraindications such as advanced portal hypertension, thrombocytopenia, or autoimmune disorders[30]. On the other hand, it is worthwhile to attempt a course of IFN-based therapy, as it has been shown in several studies that even in the absence of HBsAg loss, there is evidence that HDV RNA suppression or only reduction is associated with an improved clinical long-term outcome[11,12,31]. However, the beneficial clinical effect has to be balanced against the potential side effects. Tolerability of PEG-IFNα is a particular problem in patients with advanced liver fibrosis and PEG-IFNα is even contraindicated in decompensated cirrhosis. Thus, treatment of HDV infection in patients with the most urgent clinical need is often not possible.

In addition, late relapses beyond post-treatment week 24 have been reported[28] which mean that sustained virological response is not equal in hepatitis delta patients compared to chronic hepatitis C virus-infected patients. Treatment duration of IFN-based therapies in hepatitis delta patients was 1 year in most of the studies. Recent studies have been shown that even a prolonged antiviral treatment for 96 weeks did not lead to a higher virological response[22,32]. Predictors of response to PEG-IFNα therapy have been investigated in the past. Within the HIDIT-1 trial, HDV RNA negativity at week 24 post-treatment has been identified as the only independent factor predicting viral

Table 1. Endpoints of antiviral treatment in patients with hepatitis delta

Treatment endpoint	Parameter
Biochemical response	– ALT decline during antiviral treatment and 24 weeks after the end of antiviral treatment compared to baseline levels – ALT normalization at the end of antiviral treatment and 24 weeks after the end of antiviral treatment
Virological response	– HDV RNA decline during antiviral treatment compared to baseline levels – HDV RNA decline/negativity at the end of antiviral treatment and 24 weeks after the end of antiviral treatment
Serological response	– HBsAg decline/loss at the end of antiviral treatment and/or 24 weeks after the end of antiviral treatment – Seroconversion to anti-HBs at the end of antiviral treatment or 24 weeks after the end of antiviral treatment
Combined virological and biochemical response	– HDV RNA decline of 2 log or negativity in combination with ALT normalization at the end of antiviral treatment – HDV RNA decline of 2 log or negativity in combination with ALT normalization at week 24 after the end of antiviral treatment
Histological response	– Improvement of HAI of at least two points

HDV: hepatitis D (delta) virus.

response[33]. A subanalysis of the HIDIT-2 study showed that HDV RNA kinetics earlier than treatment week 24 was less predictive for virological response[34]. In the HIDIT trials, IFN treatment was equally effective in patients with compensated cirrhosis compared to patients with early disease[21,22]. On the other hand, data from other studies were published reporting reduced antiviral efficacy in patients with advanced liver disease[12,35]. Overall, the current guidelines recommend treatment of hepatitis delta with PEG-IFNα for 48 weeks[36]. Treatment extension is only suggested if quantitative HBsAg levels decline and HBsAg loss is a realistic option. However, this is rarely the case. In the HIDIT studies, less than 10% of patients lost HBsAg even after 96 weeks of treatment.

PEG-IFN-lambda

PEG-IFN-lambda is a type III IFN that stimulates cell-mediated immune responses that are critical for the development of host protection during viral infections. PEG-IFN-lambda targets type III IFN receptors which are distinct from the type I IFN receptors targeted by IFN-alpha (Fig. 1). These type III receptors are highly expressed on hepatocytes with limited expression on hematopoietic and central nervous system cells, which may reduce the off-target effects associated with other IFNs and improve the tolerability of PEG-IFN-lambda[37]. Although IFN-lambda does not use the IFN-alpha receptor complex for signaling, signaling through either the IFN-lambda or IFN-alpha receptor complexes results in the activation of the same Jak-STAT signal transduction cascade[38]. In a randomized, open-label multicenter trial involving 33 patients with chronic hepatitis delta, the overall tolerability was reported to be better than PEG-IFNα[39]. Lambda demonstrated comparable anti-HDV activity to historical PEG-IFNα and a dose-dependent effect was observed with lower responses when 120 microgram PEG-IFN-lambda was administered as compared to 180 microgram (mean HDV RNA decline 1.1 vs. 2.3 log IU/ml). A durable response defined as a 2 log HDV RNA decline 24 weeks after the end of treatment was observed in 36% of the patients in this trial[40]. Further studies investigating IFN-lambda for hepatitis delta have been initiated.

Treatment with HBV polymerase inhibitors

HBV polymerase inhibitors/nucleos(t)ide analogs (NAs) inhibit HBV replication only and do not have direct effects on HDV replication. Several combinations of IFNs with NAs have been tested in patients with chronic hepatitis delta. These include combinations with ribavirin[35], lamivudine[41], adefovir[21], and tenofovir[22]. As to be expected, neither adefovir nor lamivudine, tenofovir, or ribavirin showed significant effects on HDV RNA levels in patients with hepatitis delta. However, long-term monotherapy with potent anti-HBV

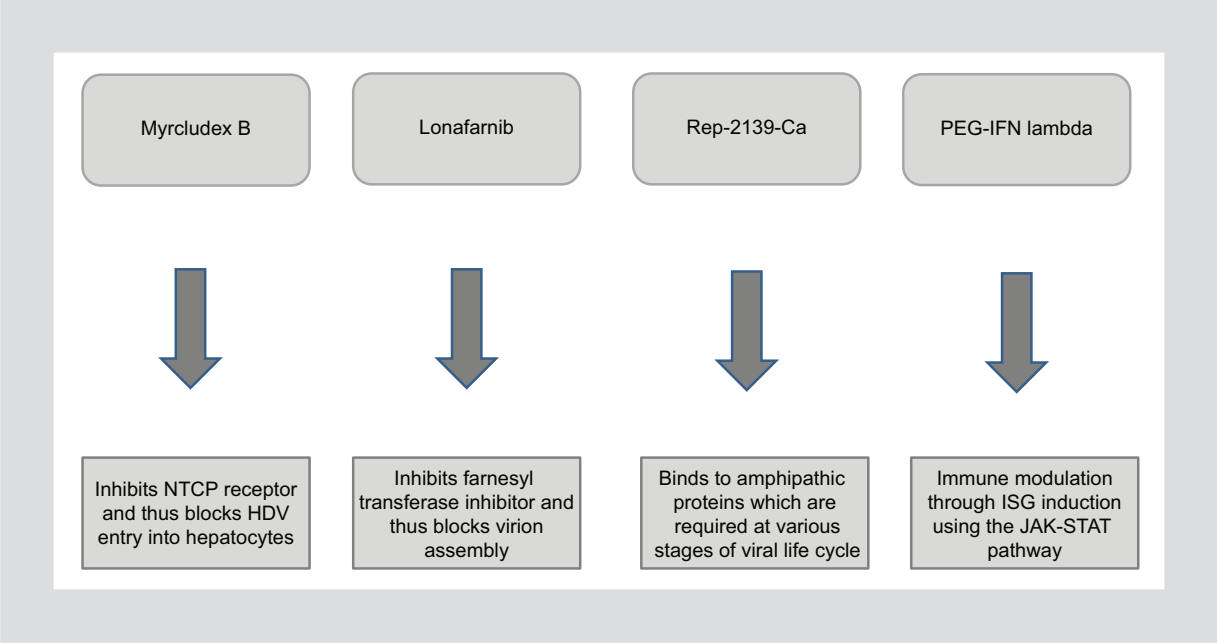

Figure 1: *Mode of action of novel antiviral drugs for Hepatitis Delta.*

drugs in patients with HIV infection has been associated with HDV RNA and even HBsAg declines in earlier studies from Spain[42,43]. The tenofovir effect on HDV RNA was independent from anti-HBV effects[43]. These findings have partially been confirmed by an analysis from the SWISS HIV cohort where also HDV RNA declines were be observed in few patients even though the majority of cases showed stable HDV RNA levels over many years in that study[44]. A potential mechanism explaining this effect of tenofovir could be the induction of IFN-lambda by tenofovir which seems to be unique to anti-HBV nucleotides[45].

Interestingly, the combination of PEG-IFN with adefovir led to a significant decrease in HBsAg levels at the end of treatment and post-treatment week 24 compared to baseline. This effect could not be observed with PEG-IFNα-2a monotherapy or with combination therapy with tenofovir in the HIDIT-2 study[22]. However, there was a trend for a better HDV RNA response to the PEG-IFN/tenofovir combination compared to PEG-IFN monotherapy[22]. In clinical practice, cirrhotic patients infected with hepatitis delta and advanced liver disease are frequently treated with HBV polymerase inhibitors to block residual HBV replication. HBV polymerase inhibitors are not yet recommended in non-cirrhotic HDV patients in the absence of HIV infection[36]. In any case, HBV polymerase inhibitors should be used if criteria for HBV treatment are fulfilled according to HBV monoinfection guidelines, for example, if HBV DNA levels are above 2000 IU/ml and/or if there is evidence of significant liver inflammation or fibrosis. As HBV DNA and HDV RNA levels can fluctuate overtime[31,46], HBV DNA and HDV RNA should be monitored regularly and antiviral therapy of HBV infection should be initiated in line with national and/or international treatment guideline of hepatitis B.

Hepatocyte entry inhibitor myrcludex B (bulevirtide)

The entry receptor sodium taurocholate cotransporting polypeptide (NTCP) has been identified as a liver-specific receptor of HBV[47] (Table 2). Myrcludex B is the first hepatocyte entry inhibitor and consists of a myristoylated lipopeptide comprising 47 amino acids of the pre-S1 domain of the HBV L-surface protein. Myrcludex B has been tested in several Phase II studies, both in HBV monoinfection and in HDV coinfection. In the first Phase 2a study, 24 HDV-infected patients were randomized into three treatment arms comparing myrcludex B 2 mg daily for 24 weeks, followed by PEG-IFNα-2a 180 µg weekly for 48 weeks (treatment Group 1), myrcludex B 2 mg daily and PEG-IFNα-2a 180 µg weekly for 24 weeks (treatment Group 2), and PEG-IFNα-2a 180 µg alone weekly for 48 weeks (treatment Group 3). The results showed that monotherapy with myrcludex B was associated with HDV RNA decline in all seven patients and two subjects became HDV RNA undetectable at treatment week 24. Interestingly, combination therapy seemed to be more effec-

Table 2. New drugs for antiviral treatment in chronic hepatitis delta

Drug	Target	Route of administration	Clinical phase	Adverse events
Bulevirtide (Myrcludex B; entry inhibitor)	Sodium taurocholate cotransporting polypeptide (NTCP)	Subcutaneous, once daily	Phase III	Transient elevation of bile acids, local side reactions; ALT increases post-treatment
Lonafarnib (prenylation inhibitor)	Farnesyl transferase inhibitor	Oral, twice daily, boosting with ritonavir	Phase III	Diarrhea, weight loss, nausea, vomiting, anorexia; ALT increases post-treatment
Rep-2139-Ca (nucleic acid polymers)	Amphipathic alpha-helices in Class I surface glycoproteins	First studies: intravenous, weekly other routes of administration to be studied (e.g., subcutaneous; daily)	Phase II	Elevation of transaminases, dysgeusia, dysphagia, hair loss
Pegylated interferon-lambda	Antiviral efficacy and immune modulation through ISG induction	Subcutaneous, weekly	Phase II	Elevation of transaminases and bilirubin (reversible)

tive as a negative HDV RNA test was obtained after 24 weeks of therapy in five of seven patients receiving myrcludex B in combination with PEG-IFNα-2a[48].

Subsequently, monotherapy with bulevirtide was investigated in a larger Phase 2b dose-finding study. Myrcludex B in combination with tenofovir dipivoxil was compared at doses of 2 mg, 5 mg, and 10 mg versus tenofovir monotherapy (myrcludex B 202 study)[49]. One hundred and twenty patients were randomized into these four treatment arms in a ratio of 1:1:1:1. Patients were pre-treated with tenofovir for at least 12 weeks. Myrcludex B was self-administered by patients once daily subcutaneously and all patients received tenofovir during the entire study period of 24 weeks. The primary endpoint, a 2 log HDV RNA decline or undetectable HDV RNA at the end of treatment, was reached by 46%, 47%, and 77% with escalating doses of myrcludex B, whereas in the tenofovir monotherapy, this endpoint was achieved by only 1 patient (3%). Interestingly, also a marked ALT decline was observed which, however, was not dose dependent as ALT normalized in 43, 50, and 40% in three myrcludex B groups. Of note and importantly, HBsAg levels did not change at all suggesting that the majority of HBsAg in patients with HDV infection is derived from HBV DNA integrated into the human genome. In addition, liver stiffness values determined by fibroscan significantly improved in the group of patients who received 10 mg myrcludex B/tenofovir versus the group of patients who received tenofovir only. As to be expected after only 24 weeks of therapy, a post-treatment HDV RNA relapse occurred in most patients and HDV RNA levels reached pre-treatment levels in most patients. Few individuals, however, maintained a partial post-treatment response with lower or even undetectable HDV RNA levels, indicating partial immune control of HDV infection. Myrcludex B was reported to be well tolerated in this study. Since NTCP is also a bile salt transporter, an asymptomatic elevation of bile acids was observed. No itching was reported by any patient in the study. Bile acid levels decreased again after stopping the study medication.

The final results of a multicenter, open-label, Phase 2 clinical trial (MYR203) to assess safety and efficacy of myrcludex B in combination with PEG-IFNα-2a in patients with chronic HBV/HDV coinfection were presented at EASL 2019[50]. Sixty patients were randomized in four treatment arms in a ratio of 1:1:1:1. Patients received 180 µg PEG-IFNα or 2 mg myrcludex B plus PEG-IFNα, 5 mg myrcludex B plus PEG-IFNα, or 2 mg myrcludex B for 48 weeks. PEG-IFNα was given once weekly and myrcludex B once daily, both as subcutaneous injection. Again, an asymptomatic, dose-dependent, and reversible increase in bile acids was observed. Median HDV RNA log reduction at week 48 compared to baseline was higher with combination treatment (–4.81 and –5.59 logs for combination with 2 mg and 5 mg myrcludex B) than with PEG-IFNα and 2 mg myrcludex B monotherapies (–1.30 and –2.84, respectively). In the myrcludex monotherapy arm, a continuous linear HDV RNA decline and ALT reduction over 48 weeks were observed. In 73.3% of patients, a

relapse occurred after the end of therapy in this arm, suggesting that longer monotherapy regimens might be required to achieve long-term control of HDV. In contrast, HDV RNA was undetectable at week 72 (24 weeks post-treatment) in 53.3% in the group of patients who received 2 mg myrcludex + PEG-IFNα and in 26.7% of the patients who received 5 mg myrcludex + PEG-IFNα. None of the patients who received PEG-IFNα monotherapy had an undetectable HDV RNA test result. Another interesting finding of this study was that a HBsAg response ≥ 1 $\log_{10}$ decline or undetectable was observed in 40% of the patients who received 2 mg myrcludex B in combination with PEG-IFNα (incl. 26.7% HBsAg loss) and in 13.3% of the patients who received 5 mg myrcludex in combination with PEG-IFNα at week 72.

The need to provide bulevirtide subcutaneously on a daily basis is a limitation which becomes more important if indefinite treatment is needed, for example, in patients with advanced cirrhosis. Long-acting formulations might be developed to overcome this issue, but clinical trials have not been performed yet with alternative formulations.

Bulevirtide showed a clear dose-dependent antiviral effect in the monotherapy trials with respect to HDV RNA declines. When combined with PEG-IFNα, there was still a dose-dependent effect on HDV RNA, but this has not been observed for HBsAg declines. There was even a trend that lower doses of bulevirtide (2 mg) led to more frequent HBsAg declines than higher doses (5 mg or 10 mg). The mechanism behind this observation is still unclear. For HBsAg decline, a loss of HBV infected is required while for the endpoint HDV RNA blocking of entry is the main mechanisms. As HBsAg declines where only found with combination treatment, PEG-IFNα is needed to delete infected cells, likely by activation of immune cells. Higher doses of bulevirtide are associated with more pronounced increases of bile acids which may lead to anti-inflammatory effects and inhibit immune cells. Mechanistic studies are currently ongoing to explore this hypothesis in more detail.

Overall, the entry inhibitor bulevirtide clearly has a dose-dependent antiviral efficacy against HDV without affecting quantitative HBsAg levels. If the drug will be used as a monotherapy, for example, in patient with advanced cirrhosis, long-term therapy for several years or even maintenance therapy will be required. Combination therapy with PEG-IFNα has curative potential for HDV infection and may even lead to functional cure of the underlying HBV infection. Future trials exploring both strategies have been initiated.

Prenylation inhibitor lonafarnib

Lonafarnib is an orally active inhibitor of farnesyl transferase. This enzyme is involved in the modification of proteins by prenylation. Prenylation of large HDAg is essential for viral assembly and secretion[51]. In mouse models, prenylation inhibitors inhibited the assembly and release of HDV, leading to rapid clearance of HDV RNA from serum[52]. In the first-in-man study, the farnesyl transferase inhibitor lonafarnib was given for 28 days in 14 patients with chronic hepatitis delta. Patients received either lonafarnib 100 mg twice daily (treatment Group 1) or lonafarnib 200 mg twice daily (treatment Group 2) of placebo for 28 days[53]. Both dosing groups showed a significant decline of mean HDV RNA levels compared to the placebo group. There were no changes in HBsAg or liver enzymes. In some patients, a HBV DNA increase was observed, indicating that HBV-DNA levels can increase when HDV RNA is suppressed. The most common adverse events of lonafarnib were gastrointestinal side effects such as diarrhea, nausea, vomiting, and weight loss. Within the subsequent Phase II studies, lonafarnib was tested as (i) monotherapy, (ii) in combination with ritonavir to boost lonafarnib levels, and (iii) in combination with PEG-IFNα.

In the lonafarnib with and without ritonavir (LOWR) HDV-1 study[54], 20 patients with compensated liver disease including some patients with cirrhosis received higher doses of lonafarnib 200 mg and 300 mg bid as monotherapy or lower doses of lonafarnib in combination with PEG-IFNα or ritonavir. Treatment duration was 8-12 weeks. Overall, the combination of low-dose lonafarnib with ritonavir or PEG-IFNα was superior concerning viral efficacy and tolerability compared to monotherapy with high-dose lonafarnib.

Within the LOWR HDV-2 study, the optimal treatment regimen was explored[55]. Fifty-five patients with compensated liver disease were included in this study. Patients received different doses of lonafarnib in combination with ritonavir or as a triple therapy in combination with PEG-IFNα. The tolerability concerning side effects were poor in the group of patients who received more than 75 mg lonafarnib twice daily in combination with ritonavir. In combination with 100 mg ritonavir twice daily, 6 months of lonafarnib 50 mg twice daily had a better antiviral efficacy than the 25 mg lonafarnib dosing group. However, the best results combining antiviral efficacy with tolerability were observed in

the group of patients who received triple combination treatment with 50 mg lonafarnib (bid) with ritonavir 100 mg (bid) and PEG-IFNα. All oral combinations with 24 weeks of lonafarnib 50 mg twice daily led to a >2 log reduction of HDV RNA at the end of treatment in 6 of 12 patients (50%). ALT normalization occurred in 7 of 10 patients with elevated ALT levels at baseline.

In the dose escalation Phase II study, LOWR HDV-4[56] patients started antiviral treatment with lonafarnib 50 mg in combination with ritonavir 100 mg bid. The lonafarnib dose was increased if patients tolerated the dose, first to 75 mg and in the second step to 100 mg, bid at 4-week intervals. Ten of 15 patients tolerated the dose escalation. At the end of treatment, mean HDV RNA decline from baseline was -1.58 ± 1.38 $\log_{10}$ IU/ml; one patient had undetectable and one patient had HDV RNA levels below the level of quantification. ALT normalized in 53% of patients; five patients had post-treatment ALT flare with normal liver function. Within the LOWR HDV-3 study, the once-daily dosing ritonavir boosting lonafarnib was explored. Lonafarnib at doses of 50 mg, 75 mg, and 100 mg qd with ritonavir 100 mg qd was administered in this study. After 24 weeks of treatment, six of 21 patients had HDV RNA levels below 250 IU/ml[57]. Finally, the side effect profile of lonafarnib required close monitoring.

The distinct reasons for flares in the lonafarnib trials are of interest. In some patients, ALT increases could be linked to HBV DNA increases or HDV RNA increases while in others, these flares occurred after withdrawal of lonafarnib. If boosting with ritonavir also contributed to flares has not been investigated in detail. Importantly, flares were usually benign and associated with virological responses, for example, HDV RNA or even HBsAg declines.

Overall, the proof of concept has been established that a prenylation inhibitor leads to HDV RNA declines in patients with hepatitis delta. Ritonavir boosting is a possibility which allows administration of lower doses. Gastrointestinal side effects are dose limiting and may also explain interindividual variability in antiviral efficacy. Both low-dose monotherapies and combination therapies with either type 1 or type 3 IFNs may option for future clinical use. A Phase 3 clinical trial has been initiated.

Nucleic acid polymers (NAPs)

NAPs are believed to block the release of HBsAg particles[58]. In addition, they may also block HDV at entry and effects seem to be independent from HBsAg escape mutations[59]. NAPs bind to amphipathic protein structures, a consequence of a hydrophobic-based interaction[60]. *In vivo* and *in vitro* studies indicated that NAPs display both entry and post-entry antiviral activity. However, HBsAg was still detectable in the liver, indicating that NAPs selectively block the release of subviral particles[61]. Phase II studies have been performed in chronic hepatitis delta patients[62,63]. In the Phase II study in chronic hepatitis delta patients, 12 patients with compensated liver disease were included and the NAP REP-2139 was given as an intravenous infusion once weekly, with add-on PEG-IFN starting at week 15 for another 15 weeks. For another 33 weeks, patients received PEG-IFN alone. HBsAg levels declined during the study in all patients and 5 of 12 patients had negative HBsAg with the development of HBs antibody titers at the end of treatment. Importantly, nine patients also had undetectable HDV RNA at the end of treatment. After 18 months post-treatment, HDV RNA was still undetectable in seven patients and five individuals were HBsAg negative[64]. Side effects were reported such as fever, peripheral hyperemia, leukopenia and thrombocytopenia, hair loss, dysphagia, or anorexia, which could be linked to PEG-IFNα. In addition, a transient ALT elevation was observed during treatment in some patients, but no patient had sustained hepatic decompensation and the "flares" may even be considered as beneficial flares in several patients. Still, more data on safety and side effects need to be provided in a larger group of patients.

Planned studies will investigate different dosing regimens including formulations allowing subcutaneous administration.

Conclusion

For patients with chronic hepatitis delta HBV entry inhibition, prenylation inhibition, block of particle formation, and IFN-lambda may represent new treatment options. Different treatment strategies can be developed. First, prolonged treatment for 2-3 years or even maintenance therapy of patients with advanced liver diseases could be the preferred option to control infection and prevent progression of liver disease. For bulevirtide, this strategy is studied in an ongoing Phase 3 trial. In contrast, finite therapies with the aim to cure HDV infection or even the underlying HBV infection may require combination with IFNs, either the well-established PEG-IFNα or with IFN-lambda. At present, Phase 2 and 3 trials are exploring this strategy for all three com-

pounds. Moreover, combination of different investigational compounds could be an alternative. For example, lonafarnib combined with bulevirtide or NAPs with bulevirtide maintenance therapy could be of interest. Transient or interval treatments may also induce HDV RNA declines in the absence of HBsAg clearance which could lead to partial immune control of HDV infection. This is not an unrealistic strategy as HDV RNA declines in the absence of HBsAg clearance have clearly been linked with improved clinical long-term outcomes[18].

Still, the short- and long-term safety for all compounds in clinical development needs to be determined in larger patient cohorts. The side effect profile differs between compounds and selection of a preferred regimen is not possible at this stage. Moreover, distinct risk groups have not been studied yet with the new drugs in development including patients with decompensated cirrhosis or HIV-coinfected patients. In this context, it has to be highlighted that lonafarnib is currently used in combination with ritonavir, but other boosters have not been studied yet. In addition, ritonavir may inhibit NTCP and thus some HIV regimens may also interfere with bulevirtide. Clearly, studies in HIV-infected patients are needed and some currently ongoing Phase 3 protocols allow inclusion of HIV-positive individuals.

Finally, it has to emphasize that the ultimate treatment goal of any antiviral treatment of HBV infection with or without HDV coinfection should be HBsAg clearance which would mean cure from both infections. Thus, novel strategies aiming to achieve HBsAg clearance including siRNA approaches or immunotherapies[23] need to be explored also in hepatitis delta.

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