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Research Article

The Hepatitis B with Delta Agent Problems of Therapy

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Abstract

Thus, to date, the only approved etiotropic drug for viral hepatitis D is - peg IFN, which is combined with nucleoside analogues in the presence of an HBV viral load. According to systematic data for example, the use of humanized mice as a laboratory model made it possible to better understand the issues of hepatitis virus replication and integration D with host cells. As a result, researchers have developed several antiviral drugs aimed at different parts of the pathogenesis of HDV infection.

Prenylation inhibitor-Lonafarnib, which blocks the exit of HDV particles from the cell; nucleic acid polymers (NAP) (REP2139Ca), an oligopeptide that mainly affects the penetration of the virus into the cell, and Myrcludex B- lipopeptide, preventing the formation of HDV RNA in initialized hepatocytes, undergoing various phases of testing in different countries.

Keywords: Hepatitis D Infection; Antiviral Therapy; Lonafarnib; Myrcludex B

Introduction

According to the world health organization (who), 257 million people live with infection caused by the hepatitis b virus (HBV) in the world, and 1.3 million patients died from its outcomes. Recent studies indicate that 33-47% of HBV-infected individuals have antibodies against the hepatitis d virus, which is estimated at about 120-160 million people [1]. A significant part (27-82%) of patients with hepatitis B with Delta agent at the time of diagnosis reveal the stage of liver cirrhosis, which is due to a more severe course and an increased risk of hepatic decompensation and hepatocellular carcinoma compared to chronic hepatitis B and C [2]. The low response to antiviral therapy, the presence of contraindications and adverse events made it necessary to develop more specific new therapeutic approaches for long-term control or, at best, functional treatment of viral hepatitis b infection with Delta agent. Due to the study of the pathogen in transgenic chimeric mice in recent years, updated data on the life cycle of HDV were obtained, which were the basis for the development of new therapeutic concepts [3].

Objective of the Study

To study current trends in antiviral therapy of viral hepatitis B with Delta agent.

Materials and Methods

Systematic reviews and meta-analyses containing the results of studies on new strategies for antiviral therapy of viral hepatitis B with Delta agent were searched in the PubMed database.

Results and Discussion

Currently, treatment options for patients with chronic hepatitis B with Delta agent are limited to interferon-alpha (IFNa) [4] and its improved derivative pegylated IFNa (pegifna) [5]. The partial

effectiveness of IFNa in patients with HDV/HBV co-infection can be attributed to two mechanically distinguishable modes of activity of this drug. First, IFNa can to some extent directly inhibit HDV replication by an as yet unspecified mechanism, as has been shown in in vitro studies (unpublished data) and in clinical trials [6]. Second, in a clinical context, interferons (IFN) can, in very rare cases, cause HBsAg clearance, possibly by cytolysis of hepatocytes of cells containing covalently closed ring DNA (cccDNA) or with integrated HBV DNA encoding HBsAg. This stable suppressed state of HBsAg is defined as a" functional cure " of both HBV and HDV infection and is achieved in less than 1% of HBeAg-negative patients [7].

To control at least the progression of HBV-related disease, nucleoside/nucleotide (an) analogues with a low barrier of resistance (for example, tenofovir or entecavir) may be considered as a possible treatment option for patients with high HBV replication [8]. It is noteworthy that tenofovir treatment in HDV/HBV-infected patients co-infected with HIV showed a marked reduction in HDV viremia [9]. Since ANS do not directly affect the auxiliary function of HBV (expression of the envelope protein from ccc or integrated HBV DNA), they cannot inhibit HDV Assembly in infected cells. Moreover, since these drugs specifically act on HBV reverse transcriptase, they do not directly affect HDV RNA replication.

Approaches to combining IFNa with nucleoside analogues to improve therapeutic outcomes have been investigated in two clinical trials. In the HIDIT-1 study, IFNa monotherapy was compared to a combination of pegifna with adefovir (ADV) - first-generation an-or ADV alone for 48 weeks. Patients tested negative for HDV RNA in 31%, 26%, and 0% of cases 24 weeks after discontinuation of the drug. Unfortunately, 56% of these HDV-negative RNA patients relapsed during long-term follow-up, which indicated that HDV clearance without negative HBsAg could not be achieved and the state of "sustained virological response" that is achieved after direct antiviral therapy in HCV patients was not observed in patients with CHD [10]. Long-term treatment with pegifna alone or in combination with tenofovir for 96 weeks (HIDIT-2 study) showed no improvement in treatment results, but the frequency of serious adverse events associated with IFNa was higher [11].

Given the serious side effects caused by IFNa, an alternative was proposed to use IFN-λ to treat a subpopulation of HDV patients who did not meet the criteria for prescribing IFNa. A clinical trial has recently been initiated to evaluate the activity of this cytokine in patients with HDV/HBV co-infection [12].

The results of studying the pathogen in transgenic chimeric mice and the obtained updated data on the HDV life cycle made it possible to develop new treatment methods aimed at controlling HBsAg secretion to reduce the auxiliary function of HBV, HBV/HDV input to prevent the formation of de novo intermediate replicative cccDNA or HDV RNA HBV for direct or indirect targeting of the replicative HDV life cycle [3,12].

The first of these, Lonafarnib, a prenylation inhibitor, prevents farnesylation of the C-terminal cys211 residue in L-HDAg by inhibiting farnesyltransferase and blocking the exit of HDV particles from the cell [13,14] (Figure 1).

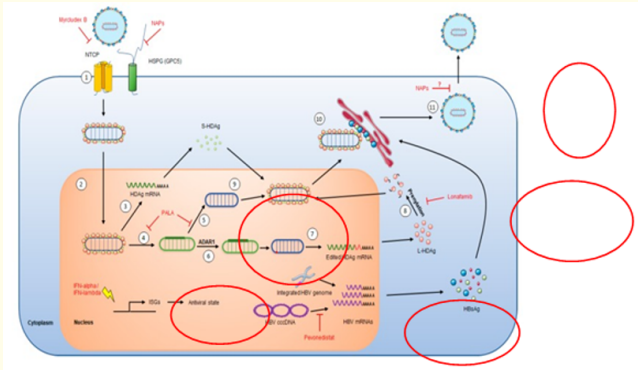

Figure 1: Points of application of antiviral drugs on HDV, 2020 (red circles).

The decrease in RNA levels in HDV serum is directly related to HDV Assembly (similar to the effect of an for HBV release) and does not primarily lead to a decrease in the number of infected hepatocytes in the liver. However, one of the effects of lonafarnib may be the acceleration of cytolysis of infected hepatocytes due to the direct cytotoxic action of accumulated replicative intermediates or enhanced immuno-mediated cell destruction. Subsequent blockade of the RNP particle envelope leads to intrahepatocellular accumulation of HDV replicative intermediates without stopping replication as such. Such possible ways of acting should be tested in future experiments. The preclinical efficacy of lonafarnib has been demonstrated in vitro and in mice [15]. Originally developed as an anti-cancer drug, Lonafarnib has been studied in several phase I and II clinical trials (Table 1) [16-18].

A short-term 4-week study described a marked dose-dependent decrease in serum HDV RNA levels. The concentration of LNF - in serum correlated with changes in HDV RNA. This study was followed by ongoing research at the Ankara University school of Medicine, Hanover Medical School, and the National Institutes of Health (NIH) in Turkey, Germany, and the United States, respectively. Three different approaches were explored on these sites.

In Ankara, the optimal dosage in combination with ritonavir (RTN) with or without peg-IFN was investigated. For the first time in the LOW-R1 study (LNF with and without RTN), LNF was tested at higher doses of 200 and 300 mg twice daily and in combination with peg-IFN or RTN. RTN enhancement increased serum LNF concentrations by a factor of 4-5. Combinations of LNF-RTN and LNF-peg-IFN resulted in a decrease in HDV serum RNA by more than 3 log 10 IU/ml from baseline after 8 weeks of treatment.

No	Medicines	Mechanism of action	Scheme of introduction	Test phase
1.	Lonafarnib	Farnesyltransferase inhibitor, inhibits the Assembly of the virion	Oral, 2-12 months± ritonavir±peg-IFN	II
2.	Рем-2139-Ca	A nucleic acid polymer that binds with a high affinity for amphipathic proteins, which are necessary at various stages of the virus ' life cycle	Intravenous infusion, once a week for 4-6 months±peg-IFN	II
3.	Myrcludex B	Prevents the penetration of hepatitis D virus in hepatocytes by inhibiting co-transportational polypeptide taurocholate sodium	Subcutaneously, daily for 6 months±peg-IFN	Ib, IIa

Table 1: Characteristics of new drugs for the treatment of chronic hepatitis D [18].

Studies on the optimal combination treatment regimen with LNF and RTN and triple therapy with LNF, RTN, and peg-IFN were tested for different periods in the LOW-R2 study. In this latest study, triple combination therapy consisting of 25 mg LNF 2 times a day with RTN 100 mg 2 times a day and peg-IFN appeared to combine better efficacy with tolerability. Three out of 5 patients were HDV RNA negative after 24 weeks of treatment. LNF at a dose of 25 or 50 mg two once a day with RTN was as effective as all oral combination medications. Five of the 14 (36%) patients had HDV RNA levels below the quantification limit after 24 weeks of treatment. The combination of LNF at doses of 75 mg twice daily and higher as a double or triple therapy was not tolerated due to side effects and also did not lead to better antiviral efficacy.

A dose-enhancing study was conducted in Hanover for LNF in combination with RTN, and the NIH investigated dosing LNF once a day with RTN. In the dose increase study, patients started with a 50 mg/100 mg LNF/RTN dose twice daily, and the LNF dose was first increased to 75 mg, and then to 100 mg twice daily at approximately 4-week intervals when patients tolerated the administered doses. The dose was no longer increased after reaching LNF/RTN (100 mg/100 mg twice daily). An increase to this final dose was possible in 10 out of 15 patients. One patient became HDV RNA negative at the end of treatment, and another had HDV RNA levels below the quantification level. Overall, it appears that in these studies, most patients lack a virological response from treatment.

A combined dosage regimen of LNF-RTN once a day for 24 weeks was tested in a double-blind approach at the NIH. Three treatment regimens were tested: LNF 50/75/100 mg per day with PTH 100 mg per day. After 24 weeks of treatment, 6 out of 21 patients had HDV RNA levels below 250 IU/ml. Interestingly, the low-dose group appeared to have better antiviral efficacy compared to higher doses. ALT normalized in all these studies with LNF in 47-75% of patients. These studies, conducted in the United States, Germany, and Turkey, provided significant data regarding optimal dosage and duration, as well as optimal combination treatment, and safety. A larger study using low-dose LNF in combination with RTN with or without peg-IFN is now needed.

The above studies confirmed previous data in cancer patients that LNF is associated with dose-dependent gastrointestinal side

effects. Therefore, based on the data mentioned above, in combination with RTN, an LNF dose exceeding 50 mg twice daily should probably not be considered. Strategies to reduce the effectiveness of treatment require further study. Along this line, the superiority of LNF and RTN combined with peg-IFN over peg-IFN monotherapy should be studied in a very well-organized study. Finally, it is necessary to investigate the possibility of inducing an increase in immunological reactivity after treatment in a group of patients with compensated and less pronounced liver disease [17].

Since lonafarnib inactivates a necessary cellular enzyme and affects important cellular signaling pathways (for example, farnesylation of molecules such as c-Ras), long-term tolerability in patients is of particular concern. LNF is associated with dose-limiting side effects, mainly gastrointestinal toxicity (Table 2).

No пп	Medicine	Adverse event
1.	Lonafarnib	Gastrointestinal toxicity (anorexia, nausea with or without vomiting, diarrhea, weight loss): depends on the dose. In cohorts with lower doses, it is usually moderate and well tolerated
2.	Рем-2139-Ca	Hair loss, dysphagia, anorexia, dysgeusia in the hepatitis B study: associated with exposure to heavy metals at the test site Side effects associated with administration: grade 1 peripheral hyperemia, fever, chills, and headache
3.	Myrcludex B	Increased lipase and amylase in phase I, but not in phase II study Increased levels of bile acids conjugated with taurine and glycine, without obvious clinical consequences Thrombocytopenia, neutropenia, lymphopenia, and eosinophilia: usually mild, transient

Table 2: Adverse events of new drugs for the treatment of chronic hepatitis D [18].

These side effects include anorexia, nausea, diarrhea, and weight loss. Finally, in the LOW-R2 study, 5 out of 27 patients treated with LNF in combination with ritonavir, a CYP3A4 inhibitor for 12-24 weeks, experienced an increase in ALT after treatment against the background of HDV RNA suppression below the quantification level. In this case, Lonafarnib was tolerated longer, which led to a decrease in the viral load to 3 log10 [18].

In a subsequent ongoing study (LOWR HDV-2), patients received additional reduced doses of lonafarnib (75 mg, 50 mg, or 25 mg twice daily) in combination with ritonavir and with or without pegifna for 12-24 weeks. In terms of virological responses, triple therapy using 25 mg lonafarnib, 100 mg ritonavir, and pegifna showed a reduction in HDV RNA below the quantification limit in 5/5 patients at week 24. It will be interesting to observe the progress of HDV RNA levels and the possibility of a sustained response after drug withdrawal. In addition, it will be difficult to clinically control the side effects associated with lonafarnib if a "functional cure" cannot be achieved and indefinite treatment periods are required.

Nucleic acid polymers (NAP) (REP2139Ca) are a diverse group of oligonucleotides that have been described as agents with a wide range of antimicrobial activity, including inhibition of HIV, herpes simplex virus, or Cytomegalovirus infection [19] (See figure 1). the Initial proposed mode of action was the interaction of NAP with molecules involved in stimulating virus penetration (for example, heparan sulfate proteoglycans). As for their antiviral activity against hepadnaviruses, individual NAPs were tested in the hepatitis b virus model system. These studies showed that one compound (REP2006) mainly affected viral penetration, while another compound (REP2055) affected DHBV even after infection was established, leading to drug accumulation in duck hepatocytes and suppression of s-Ag secretion of duck hepatitis b virus [20].

Based on the results obtained in the DHBV model, the first two clinical trials were conducted on monoinfected HBV patients. The first phase I/II human study was conducted in Bangladesh. It was reported that seven of the 8 HBeAg-positive CHB patients treated with REP-2055 had a 2 - 7 logarithm decrease in HBsAg, and three of them subsequently had HBsAg clearance. All 7 patients developed anti-HBsAg titers. The serum hepatitis b virus DNA decreased by 3-7 log after 20-27 weeks of treatment. Three patients stopped treatment at 20-27 weeks according to the early termination Protocol (HBsAg loss or HBeAg loss). After treatment, 1 patient had a viral and serological return, while the other 2 patients had negative results for HBV and HBsAg DNA. However, intravenous injection of REP-2055 was accompanied by fever, chills, and headache.

REP 2139-Ca, which was reported to be more stable, was given once a week by intravenous infusion to 12 patients with HBeAg-positive CHB. Nine Respondent patients (reduced HBsAg and HBV

DNA by 2 log) received additional peg-IFN or thymosin after 20 weeks. With monotherapy, 9 patients had a decrease in HBsAg from 2 to 7 log, and three patients had a negative HBsAg, and there was also a decrease in HBV DNA in the blood.

REP-2139-Mg and REP-2165-Mg, a derivative of 2139 C, were tested in combination with peg-IFN and tenofovir in 20 patients with HBeAg-negative CHB who previously received a 6-month course of tenofovir. Data from the study indicate a similar decrease in HBsAg levels, and in 5 out of 12 patients, HBsAg remained negative for 1 year after treatment. In addition to the side effects associated with taking the drug, such as fever, chills, and peripheral hyperemia, other reported side effects include anorexia, hair loss, dysphagia, and dysgeusia, which researchers have linked to the effects of heavy metals (See table 2).

Post-treatment results were presented at the EASL meeting in 2017. Since the results of these trials showed a significant reduction in HBsAg levels in the serum of hepatitis B patients, NAP REP2139-Ca was tested in chronic HDV-infected patients (REP301). Monotherapy of 500 mg REP2139-Ca (in/in 1 time per week) for 15 weeks followed by a combination of 250 mg of the drug with 180 mcg of pegifna for another 15 weeks was received by 12 patients with HBV/HDV co-infection. Pegifna was maintained for another 33 weeks, and patients were followed up for 24 weeks after discontinuation of the drug. Intermediate results showed a strong decrease in the level of HDV RNA in serum, accompanied by a marked decrease in the level of HBsAg in serum. Recent in vitro data indicate that the inhibitory effect of the selected NAP is provided by a modification of the 2'-OH ribose by a methyl group that cancels the penetration of HBV. Thus, inhibition of entry can be excluded as the mode of action of REP2139 (which is a 2 ' O-methyl-ribose derivative) when tested on HDV. In the same study, there was no inhibition of HBsAg secretion by REP2139 in HBV-infected HepaRG cells, which raises the question of how the drug causes the observed decrease in HBsAg serum levels in patients. Adverse events were also noted (See table 2). a Detailed summary of the data presented can be found on the company's website [19,21].

large randomized controlled trials are currently expected, in which the effectiveness and duration of response to treatment can be evaluated for both monotherapy and combination treatment.

Myrcludex B, a subcutaneously administered synthetic lipopeptide, a lead substance characterized by hepatotropism, specifically binds hNTCP in the liver and thereby prevents the de novo formation of HDV RNA and cccDNA in naive and regenerating hepatocytes of humanized mice and chimpanzees at subnanomolar concentrations [22-24] (See figure 1). due to inhibition of the bile acid Transporter function, NTCP causes an increase in the level of conjugated Bile acids in humans when administered at doses > 3 - 4 mg/person [25-27] (See table 2). Increased bile acid levels were also randomly identified, but without obvious clinical syndromes [28,29].

Myrcludex B successfully passed phase I of safety studies [30] and entered phase IIa of clinical trials (Myr-201) on HBeAg-negative patients with HBV and HBV/ HDV co-infection [31,32]. In a study involving 24 patients with HDV/HBV co-infection, Myrcludex B was administered at a low, non-NTCP saturating dose (2 mg per day), either alone or in combination with pegifna for 24 weeks. Only Pegifna was used as a control. Myrcludex B was well tolerated, and only a small increase in bile salts was observed. At week 24, HDV RNA decreased by more than 1 log in all groups and became negative in two patients, each of whom was in the control group Myrcludex B and pegifna. It is noteworthy that a negative reaction was observed in five of the seven evaluated patients of the combined group Myrcludex B/pegifna, which indicates a synergistic effect of pegifna and Myrcludex B. HBV DNA levels were significantly reduced at week 24 in the Myrcludex B/pegifna cohort.

Currently contains two multi-center studies with higher doses Marklogic V. In the Myr-202 study (n = 120), the drug was administered over 24 weeks in 3 different doses (2 mg, 5 mg, and 10 mg) in combination with tenofovir compared to tenofovir alone.

The second study (Myr-203) combines two doses of Mirkludex B (2 mg and 5 mg) with IFNa for 48 weeks compared to only Mirkludex B or IFNa. All three drugs are evaluated separately or in combination with pegifna and/or an similar to tenofovir, but - so far - not in combination with each other. Follow-up trials for all three drugs are ongoing and are expected to be presented immediately at upcoming meetings of the liver research societies (AASLD, EASL). Detailed research results and interim results presented at previous meetings are summarized in a recent review [33].

Responding to the urgent medical need for new drugs for chronic hepatitis D, Lonafarnib and Myrcludex B have been recognized by the European medicines Agency (EMA) and the US food and drug Administration (FDA). Lonafarnib received "Accelerated

status" from the FDA in 2015, and Myrcludex B received" primary compliance status " from the EMA in may 2017.

Additional approaches to the treatment of hepatitis B with Delta agent. Another area of therapy is the use of small interfering RNAS (miRNAs). ARC-520, a miRNA designed to reduce all HBV transcripts by RNA interference, a dose-dependent reduction in HBsAg levels after a single injection of HBeAg-negative patients with CHB was obtained in a phase IIa clinical trial. Multiple extended studies (up to 12 doses once a month) of the same compound were conducted. With repeated administration, it was observed additional reduction in HBsAg levels, and to a greater extent in HBeAg-positive than in HBeAg-negative patients.

However, it was reported that ARC-520 is well tolerated, but the study was suspended due to toxicity problems associated with the carrier molecule. MiRNA and various immunological approaches to treatment are evidence-based treatments. They are based on a solid scientific Foundation.

We know, for example, from hepatitis B that removing the virus after treatment requires strict immune control, so it makes sense to use an immune approach to control of HCG. The lack of success so far indicates the complexity of the immunological process. Similarly, siRNAs are noteworthy, since multiple siRNAs targeting different pregenomic RNAS can be used with the same composition.

However, both the immunological and oligonucleotide approaches require time to further develop these approaches. Thus, to date, the only approved etiotropic drug for viral hepatitis D is - peg IFN, which is combined with nucleoside analogues in the presence of an HBV viral load. According to systematic data for example, the use of humanized mice as a laboratory model made it possible to better understand the issues of hepatitis virus replication and integration D with host cells. As a result, researchers have developed several antiviral drugs aimed at different parts of the pathogenesis of HDV infection.

Prenilation inhibitor-Lonafarnib, which blocks the exit of HDV particles from the cell; nucleic acid polymers (NAP) (REP2139Ca), an oligopeptide that mainly affects the penetration of the virus into the cell, and Myrcludex B-lipopeptide, preventing the formation of HDV RNA in initialized hepatocytes, undergoing various phases of testing in different vaccines.

Conclusion

The results of clinical studies show encouraging data on the effectiveness of drugs, while there are pronounced side effects, which forces researchers to combine several groups of antiviral drugs and test their different dosages. In this regard, it is highly likely that one of the mandatory components of combined anti-viral therapy peg-IFN will perform. Unfortunately, this situation does not allow patients to avoid the undesirable effects of interferon therapy, even when using new strategies for treating viral hepatitis B with Delta agent.

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