Management of HBV and HBV/HDV-Associated Liver Cirrhosis

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Keywords

Hepatitis B · Hepatitis D · Liver cirrhosis ·
Hepatocellular carcinoma · HCC ·
Nucleos(t)ide analogues · Pegylated interferon

Summary

Background: Chronic hepatitis B virus (HBV) infection and hepatitis delta virus (HDV) co-infection lead to liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC). **Methods:** We review the current knowledge of the management of HBV mono-infection and HBV/HDV co-infection with a special emphasis on liver cirrhosis. **Results:** Treatment options for chronic hepatitis B are pegylated interferon (PEG-IFN) alfa and nucleos(t)ide analogues (NUC). PEG-IFN is a finite option to achieve hepatitis B surface antigen loss in compensated cirrhosis. However, this goal is rare. NUC are potent to achieve HBV DNA suppression but long-term treatment is mandatory in most cases. Long-term treatment with NUC can lead to reversion of liver cirrhosis, improve liver function, prevent liver transplantation, and reduces but does not eliminate the risk for development of HCC. Treatment options for hepatitis D are limited to PEG-IFN. Although late relapse is common, treatment with PEG-IFN reduces disease progression. However, new treatments are urgently needed for HDV infection. **Conclusion:** Early treatment of chronic hepatitis B and D is important to prevent complications of cirrhosis. HCC surveillance remains important in patients with cirrhosis.

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Introduction

Recent estimations for the world-wide prevalence of hepatitis B virus (HBV) infection assume that about 248 million people are chronically infected [1]. Sequelae of chronic HBV infections are liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC). Half of the mortality associated with liver cancer can be attributed to HBV infection [2]. The challenges in the optimal management of chronic HBV infection are the decisions whom to treat, how to treat, and when to start and stop treatment. A good understanding of the risk factors associated with an adverse course of HBV/hepatitis delta virus (HDV) infection as well as the natural course of the disease is a prerequisite. The major risk factors for the development of cirrhosis and HCC are high levels of HBV DNA [3], older age, male gender, family history of HCC, hepatitis B e antigen (HBeAg) serostatus, high alanine aminotransferase (ALT) levels, high quantitative hepatitis B surface antigen (HBsAg) levels, basal core promoter mutations, and HBV genotype C [4]. However, the natural course of chronic HBV infection is highly variable and can be classified into three distinct phases. The first phase of vertically transmitted HBV infection is characterized by a so-called ‘immuno-tolerance phase’ with high HBV DNA levels and normal ALT values, which lasts up to 20–30 years. Normal ALT values despite high HBV DNA is explained by the fact that HBV is not cytopathic and liver damage as well as viral control is mediated by the immune system [5]. Nevertheless, the concept that the immune system is ‘tolerant’ has recently been challenged by data showing that HBV exposure in utero triggers a state of trained immunity [6]. Later on, the immune response towards HBV alters and the natural course of HBV infection proceeds to the immunoactive phase, during which the immune system tries to control the virus. This phase is characterized by high ALT levels and decreasing HBV DNA. HBsAg drops in response to the ongoing immune response. Recurrent immune-mediated flares may cause the development of cirrhosis and HCC [7]. However, many patients in the immune clearance phase can develop anti-HBe seroconversion. After anti-HBe seroconversion,

Fig. 1. Response rates of patients with advanced fibrosis and liver cirrhosis 24 weeks after the end of PEG-IFN therapy [19, 22]. ISHAK score was used to quantify the degree of liver fibrosis.

immune control is achieved and the infection proceeds to an inactive carrier state with low HBV DNA and low risk for progression. However, reactivation of active hepatitis is possible at any time [8, 9], most frequently due to escape mechanisms. This leads to HBeAg-negative active hepatitis. Commonly, precore mutations or basal core mutations are present in these patients, which also have an increased risk for disease progression [10]. If left untreated, the incidence of cirrhosis in patients with HBV infection is estimated to be 838.1 per 100,000 person-years in a study from Taiwan [4]. In cirrhotic patients, the annual incidence of HCC is projected to be 2–3% [11]. The association of viral load and complications of HBV infection has been shown in the REVEAL study for patients older than 30 years who were not in the first ‘immunotolerance phase’ [3]. HBV DNA levels >2,000 IU/ml are associated with a cumulative incidence of HCC of 3.57% after 13 years. With higher viral loads, the risk for HCC increases. HBV DNA of >20,000 IU/ml is associated with a risk for HCC of 12%. Accordingly, the main focus of treatment in chronic HBV infection is the prevention of cirrhosis, HCC, and hepatic decompensation by reducing HBV DNA and subsequently hepatic inflammation [12].

Co-infections with other viruses such as HCV or HIV due to similar transmission routes have to be considered in patients with hepatitis B. One co-infection, which is unique only for HBV infection, is HDV co- or super-infection. HDV infection can occur simultaneously as acute HBV and HDV co-infection, but also at any time point during chronic HBV infection. HDV is a small RNA virus that is dependent on the presence of HBsAg for transmission. It is estimated that between 15 and 20 million people are chronically infected with HDV world-wide [12–14]. HDV superinfection leads to a severe aggravation of liver disease and faster progression to cirrhosis and hepatic decompensation [14, 15]. Importantly, HDV infection leads to the suppression of HBV infection in most patients and the long-term clinical outcome is irrespective of the HBeAg status of the patient [15].

Both HBV mono-infection and HBV/HDV co-infection can cause the development of liver cirrhosis and hepatic decompensation. In this review, we summarize what is currently known about the management of HBV and HBV/HDV infection in these patients with advanced liver disease.

Treatment of Chronic Hepatitis B

Current treatment of chronic HBV infection is based on two treatment options, i.e. pegylated interferon (PEG-IFN) alfa or nucleos(t)ide analogues (NUC) [12]. Treatment with PEG-IFN is a finite treatment and aims for sustained immune control off-treatment. For HBeAg-positive patients sustained immune control is defined by anti-HBe seroconversion and HBV DNA < 2,000 IU/ml. For HBeAg-negative patients sustained immune control is defined by HBV DNA < 2,000 IU/ml and normal ALT [16]. Most studies define these end points 6–12 months after the end of therapy. In contrast to PEG-IFN, treatment with NUC aim for sustained viral suppression on treatment. As treatment with NUC has only limited effects on covalently closed circular DNA replenishment, long-term treatment is mandatory in most patients. Whereas the indication for antiviral treatment in non-cirrhotic patients is based on HBV DNA > 2,000 IU/ml and signs of hepatitis [12, 17], indication for antiviral treatment in cirrhosis is independent of HBV DNA. Due to the highly dynamic natural course of HBV infection with the risk of reactivation and subsequent hepatic decompensation, all cirrhotic patients with detectable HBV DNA in highly sensitive assays should receive treatment [12, 17].

Treatment of Chronic Hepatitis B and Cirrhosis with PEG-IFN

Several studies have demonstrated the efficacy of PEG-IFN in the treatment of HBV infection in HBeAg-positive and HBeAg-negative patients [18–20]. The recommended treatment duration is 48 weeks at a dosage of 180 µg once weekly for PEG-IFN alfa-2a. In HBeAg-positive patients, the main goal is to achieve anti-HBe seroconversion and/or anti-HBe seroconversion with normalized ALT. The main reasoning is the finding that anti-HBe seroconversion after IFN treatment is associated with a significantly increased likelihood of survival [21]. About one third of the patients achieve a sustained anti-HBe seroconversion 6 months after end of treatment [12, 17]. In HBeAg-negative patients, success of therapy is defined by HBV DNA < 2,000 IU/ml and/or normalized ALT. Normalization of ALT was achieved in 59% of patients, and a reduction of HBV DNA < 2,000 IU/ml was seen in 19% of patients [22]. Importantly, subanalysis of the phase III studies of PEG-IFN

Fig. 2. Management of hepatitis B infection and liver cirrhosis.

showed a similar or even better efficacy in patients with compensated cirrhosis (fig. 1).

One major advantage of PEG-IFN treatment are the immunomodulatory effects which have considerable beneficial effects even years after the end of therapy. After a median follow-up of 8.8 years, HBsAg loss of 52% was described in a study of HBeAg-positive patients responding to IFN treatment [16]. Overall, HBsAg seroclearance is the event which is considered to be the best equivalent of cure for HBV infection to date and is associated with the lowest risk for complications [12, 23].

The downside of PEG-IFN treatment are severe side effects. Thus, several attempts to predict treatment response at baseline have been made. Next to the established factors low HBV DNA ($<10^8$ IU/ml), higher ALT ($>2-5 \times$ ULN), and HBV genotypes A and B [12, 17] (fig. 2), HBsAg levels at the start of treatment are associated with a better treatment response [24]. However, HBsAg is a better tool for predicting response during treatment with PEG-IFN. This is especially important in order to predict treatment failure and discontinue treatment prematurely to reduce side effects [25, 26]. In HBeAg-positive chronic HBV infection, no decline of HBsAg at week 12 of treatment and an HBsAg $> 20,000$ IU/ml are highly predictive for treatment failure defined as failing anti-HBe seroconversion [27–29]. Thus, treatment should be withdrawn in these patients. In contrast, HBsAg $< 1,500$ IU/ml at week 12 of

treatment had a positive predictive value for anti-HBe seroconversion and subsequent HBsAg seroclearance [28]. Also in HBeAg-negative chronic HBV infection, a decline of HBsAg until week 12 of treatment (>0.5 log) predicted a treatment response [30]. If no HBsAg decline was achieved and HBV DNA did not decline >2 log, no treatment response could be achieved [31].

For patients with cirrhosis, HBsAg loss should be the main goal if PEG-IFN is considered. If HBV DNA remains positive (even if $<2,000$ IU/ml) after the end of therapy or during follow-up, treatment with NUC should be initiated.

In decompensated cirrhosis, PEG-IFN is contraindicated due to the possible risk of inducing flares and causing acute-on-chronic liver failure. Accordingly, patients with decompensated cirrhosis should only be treated with NUC (fig. 2).

Treatment of Chronic Hepatitis B and Cirrhosis with NUC

Current guidelines recommend to use entecavir or tenofovir in patients with cirrhosis due to their higher barrier for resistance [12, 17]. More than 90% of patients achieve HBV DNA suppression after 5 years of treatment [12, 17], irrespective of liver fibrosis stage. Treatment failure is mainly due to noncompliance. Resistance to entecavir is less than 1% in lamivudine-naïve patients, and no resistance has been documented for tenofovir so far [12, 17]. The aim for treatment with NUC is complete suppression of HBV

Fig. 3. Efficacy of tenofovir (TDF), emtricitabine (FTC)/TDF, or entecavir (ETV) in a double-blind, randomized phase II trial of 112 patients with decompensated cirrhosis after 48 weeks. Patients with <2 log decrease of HBV DNA at week 8 or >1 log increase above nadir or 400 copies/ml HBV DNA at 2 time points after having HBV DNA < 400 copies/ml or > 400 copies/ml at week could be switched to open label FTC/TDF and were counted as treatment failures. 6 patients underwent (preplanned) liver transplantation and were excluded from analysis. *Only for patients with initial Child-Turcotte-Pugh (CTP) score ≥ 7 (modified from [42]).

DNA on treatment but also immunological control, which results in the possibility of stopping NUC treatment. Sustained off-treatment response may be defined as HBV DNA < 2,000 IU/ml (for cirrhosis < lower limit of detection) for more than 12 months after treatment discontinuation. In HBeAg-positive patients, treatment may be discontinued after anti-HBe seroconversion and a consolidation therapy of 12 months. However, relapse and HBeAg reversion have to be considered [9]. Thus, NUC discontinuation even after anti-HBe seroconversion may be dangerous in HBeAg-positive patients with liver cirrhosis. In patients with liver cirrhosis, stop of therapy after anti-HBeAg seroconversion may only be considered in a safe and stable situation, i.e., if there is evidence of reversion of cirrhosis, as discussed in the following (fig. 2). For HBeAg-negative patients, no rules for treatment discontinuation are currently established [12]. In patients with cirrhosis, treatment should be continued indefinitely due to the risks of flares and hepatic decompensation after treatment withdrawal.

Guidelines suggest discontinuing NUC treatment after HBsAg seroclearance. For patients with cirrhosis we would only recommend this approach in a stable situation (anti-HBs seroconversion to titers > 100 U/l) because HBsAg reversions can occur [12]. The new concept of stopping NUC treatment before HBsAg seroclearance in HBeAg-negative patients [32, 33] should not be pursued in cirrhotic patients because of the risk for flares and hepatic decompensation. In general, HBsAg loss and seroconversion to anti-HBs is a rare event during NUC therapy [23, 34]. Monitoring of HBsAg levels during NUC treatment may predict later HBsAg loss. For example, decline of HBsAg > 1 log within the first year of treatment or > 0.5 log within 2 years after HBV DNA suppression are predictive for later HBsAg seroclearance [26].

Effect of Antiviral Therapy on Fibrosis and Cirrhosis Regression

Treatment of HBV infection in patients with fibrosis and compensated cirrhosis can lead to histological regression. Chang et al. [35] studied the effect of entecavir in 57 patients with a median follow-up of 6 years. 88% of all patients had regression of fibrosis and all patients with cirrhosis at the time of inclusion (7% of the study population) showed histological improvement. Marcellin [36] et al.

showed similar data for tenofovir in a larger cohort of 348 patients in which 97 patients (28%) had cirrhosis at baseline. After 5 years histological regression was found in 74% of all cirrhotic patients. Interestingly, the main factor that reversion of cirrhosis did not occur was obesity. Regression of fibrosis was also shown in other studies. One study showed improvement of liver fibrosis/cirrhosis in 43–59% of patients treated with entecavir ($n = 120$) and in 33–53% of patients treated with lamivudine ($n = 125$) after 48 weeks. No major difference was found between HBeAg-positive and HBeAg-negative patients [37]. Another study demonstrated that long-term telbivudine treatment with profound and durable viral suppression significantly improved liver histology [38]. This study also confirmed that non-invasive analysis of liver stiffness by elastography could be used to track improvement of fibrosis.

Treatment of Chronic Hepatitis B and Decompensated Cirrhosis

Decompensation of liver cirrhosis is marked by the development of hepatic encephalopathy, ascites, or gastrointestinal bleeding. The frequency of decompensation varies in the presence of viremia in patients with cirrhosis and is estimated to be 1% in non-viremic patients and 4% in viremic patients annually [39]. Prior to NUC therapy, compensated cirrhosis had a 5-year survival of about 80%; however, it was markedly reduced, i.e. about 14%, in decompensated cirrhosis [40].

Several trials have demonstrated the value of NUC treatment in decompensated cirrhosis. A meta-analysis of 13 trials including 873 patients with decompensated cirrhosis demonstrated that NUC treatment with either entecavir or lamivudine reduces mortality in addition to the strong antiviral efficacy [41]. The rate of HBV DNA undetectability was higher for entecavir across 8 of the 13 studies, which assessed HBV DNA undetectability at week 12, 24, and 48. No difference between the newer NUC tenofovir, emtricitabine/tenofovir, and entecavir could be shown in a randomized double-blind study in patients with decompensated cirrhosis (fig. 3) [42]. Thus, entecavir and tenofovir are equally effective. Combination of entecavir and tenofovir showed no additional benefit in a randomized study in patients with multiple drug failure, although only 18% of patients were cirrhotic [43].

The overall survival of decompensated cirrhosis with NUC treatment was strongly improved. In a multicentric, double-blind, randomized trial with 228 participants (Child-Pugh class A: 18, B: 155, C: 55) the survival after 104 weeks was 79% for lamivudine and 87% for telbivudine [44]. Most deaths in the setting of hepatic decompensation occurred within the first year, and, not surprisingly, baseline liver function was the main predictor for mortality [45].

Importantly, treatment of advanced HBV infection leads not only to improved survival but also to restoration of liver function. This is especially apparent in decompensated cirrhosis. In a study with 70 patients with decompensated cirrhosis receiving treatment with entecavir, the Child-Pugh score decreased from 8.1 before treatment to 6.6 after 12 months of treatment. Overall, 65.5% of patients with decompensated cirrhosis reached the compensated status Child-Pugh A. The model for end-stage liver disease (MELD) score decreased from 11.12 to 8.8 in this time period [46]. Similar improvements in the Child-Pugh score were shown in the study by Liaw et al. [42] (fig. 2). Furthermore, treatment can also increase the transplant-free survival and may lead to delisting in some patients. In one prospective multicenter study with 707 participants the transplant-free survival was 59.7% in the treated cohort in comparison to 46% in the untreated cohort. One third of the treated patients could be delisted from liver transplantation on follow-up [47].

However, a significant difference in the long-term outcome between patients who are responding to treatment and those who show no or only a partial response could be observed [46]. Although an initial improvement in liver function could be seen in all patients receiving antiviral therapy, about 1 year after treatment initiation the liver-related mortality in non- or partial responders was as high as in untreated patients [48]. In contrast, complete virological response defined by HBV DNA < 80 IU/ml was associated with a better clinical outcome (hazard ratio for disease progression 0.29). The severity of the liver disease did not reduce the chance of virological response. However, low-level viremia with HBV DNA < 2,000 IU/ml without complete virological response was already associated with a diminished clinical outcome [49]. Thus, cirrhotic patients should be monitored for complete virological response. In patients with a failure to NUC monotherapy, a rescue therapy with the combination of entecavir and tenofovir may increase the likelihood of achieving complete virological suppression [50]. However, most trials had no control groups.

In general, NUC treatment is safe and well tolerated in decompensated cirrhosis [41]. However, Lange et al. [51] reported some cases of lactate acidosis with entecavir in patients with advanced MELD scores >22. Lactic acidosis resolved after treatment interruption. Thus, patients with advanced liver disease should be closely monitored and treatment should be interrupted if signs of lactic acidosis are observed.

Effect of Antiviral Therapy on HCC Development

HBV infection is one of the major risk factors for the development of HCC. In patients with cirrhosis the incidence of HCC is

estimated to be between 1.2 and 2.7% per year in the natural course [52, 53]; however, the incidence is strongly influenced by region, age, stage of the liver disease, and other comorbidities.

Many studies have analyzed the effect of antiviral treatment on HCC development, and most studies show that NUC therapy can reduce the risk for HCC. In one meta-analysis the effect of IFN therapy on the development of HCC was assessed. In total, 2,742 patients from 12 studies were included. The risk for HCC development was reduced by 34% after IFN therapy in comparison to controls. Importantly, the risk reduction was higher in cirrhotic patients [54]. In 2,289 patients from 5 studies receiving NUC therapy the risk for HCC was reduced by 78% in comparison to controls. A larger meta-analysis by Papatheodoridis et al. [55] including 3,881 patients treated with NUC and 534 patients without treatment from 21 studies showed an incidence of HCC in 2.8% of treated patients and of 6.4% of untreated patients after a follow-up of 46 months. The presence of cirrhosis was identified as one of the main risk factors for HCC development.

These findings have been validated in studies showing a 5-year incidence for HCC of 7–13.8% with antiviral therapy and of 26.4–38.9% without antiviral therapy in cirrhotic patients [56]. However, this data is derived from Asian patients and no direct comparison between treated and untreated patients in Caucasian patients is available to date. Nevertheless, data from the European VIRGIL network confirmed a similar HCC incidence of 10.9% for cirrhotic patients with antiviral therapy after a 5-year follow-up [57]. Thus, it is important to note that there remains a significant risk for HCC in cirrhotic patients despite HBV DNA suppression.

In addition to the presence of cirrhosis, the early and durable virological response to antiviral therapy is another key factor that determines the risk for the development of HCC [55]. In a study with 872 patients treated with lamivudine for at least 1 year, the annual incidence of HCC was 0.95% in patients with virological response in comparison to 2.18% in patients with viral breakthrough and 5.26% with persistently elevated HBV DNA [58]. In this study, risk reduction for the incidence of HCC could be seen in patients with compensated cirrhosis but not in decompensated cirrhosis. However, the time to HBV negativity seems to be one predictor, especially in more advanced cirrhosis. In one study of 209 patients treated with entecavir, a significant reduction in the incidence of HCC was seen in patients with decompensated cirrhosis if virological response was achieved within 12 months [59]. Overall, data hints that a further reduction in the incidence of HCC can be achieved with early treatment and the induction of a rapid virological response. However, HCC surveillance remains important in cirrhotic patients because the HCC risk cannot be eliminated (fig. 2) [60].

To optimize the surveillance it is helpful to predict the risk based on scores. Different scores in different settings have been suggested, i.e. GAG-HCC [61], CU-HCC [62], REACH-B [63], and PAGE-B score [64]. The risk assessment is based on patient (age, gender, cirrhosis, platelets) as well as viral factors (HBV DNA). The main value is the high negative predictive value of the scores to exclude HCC development within 3–10 years. Patients with low scores may

not require close monitoring. The positive predictive value of all scores was below 25%; thus, these scores cannot identify patients with a very high risk for HCC. However, it is important to note that these scores have some limitations. Several additional markers, which have been shown to have predictive value for the risk for HCC development (i.e. quantitative HBsAg, HBV genotype), are not included in the aforementioned scores [65]. The GAG-HCC, CU-HCC, and REACH-B scores were derived from untreated patients. Antiviral therapy strongly affects the viral factor and thus leads to an overestimation of the incidence of HCC. In addition, the performance of these scores was lower in Caucasian patients in comparison to Asian patients [57]. Only recently, Papatheodoridis et al. [64] developed and validated the PAGE-B HCC risk score in >1,800 Caucasian patients treated with the current first-line NUC entecavir and tenofovir for >12 months. The PAGE-B risk score is based on the patient's age, gender, and platelet count without the need for any complicated mathematical calculation and is therefore easy to use in routine clinical practice. Despite all scores, the cornerstone for the detection of HCC remains regular screening with ultrasound every 6 months in patients with liver cirrhosis (fig. 2) [60]. Whether the intervals of screening can be modified according to risk scores needs to be discussed in future guidelines.

Treatment of Hepatitis Delta

Superinfection with HDV has detrimental effects on the course of the liver disease. When compared to HDV-negative patients, HDV-positive patients with compensated cirrhosis have their risk for HCC, decompensation, and mortality increased by the factor of 3.2, 2.2, and 2.0, respectively [66]. However, it is unclear whether HDV induces HCCs directly or indirectly. HDV is able to modify DNA methylation which could be directly carcinogenic [67]. In contrast, the increased development of cirrhosis in hepatitis D may already explain the higher frequency of HCC in individuals co-infected with HDV irrespective of direct oncogenic effects [68]. Thus, patients with hepatitis D have an urgent treatment indication [12]. Obviously, the main goals are prevention of disease progression and prevention of HCC. However, no definite clinical end point has been defined.

The problem is that effective therapies for hepatitis D are missing. The HDV does not code for its own enzymes; therefore, possible direct-acting antiviral targets are difficult to identify. So far, treatment options are limited to PEG-IFN. The currently suggested treatment for patients with HDV infection is 180 µg PEG-IFN alfa-2a given for 48 weeks once weekly. In contrast to HBV mono-infection, there is no established stopping rule. Virological response rates defined by HDV RNA negativity 6 months post treatment were only around 25% in the pivotal HIDIT-1 trial [69]. Importantly, more than half of the HIDIT-1 patients with a post-treatment HDV RNA response – which was initially considered to be a 'sustained' virological response (SVR) – relapsed during further long-term follow-up [70], demonstrating that the term SVR should not be used in the context of PEG-IFN treatment of HDV

infection. Thus, regular follow-up visits after the end of therapy are required. However, an early off-treatment response seems to be clinically beneficial as none of the patients with a post-treatment HDV response in week 24 developed liver-related clinical end points during 5 years of follow-up, even if virological relapse was evident [70]. These findings further suggest that successful PEG-IFN treatment translates into a beneficial clinical long-term outcome which is also supported by findings from the Greek-Hep-Net cohort [14]. Some studies evaluated a prolonged treatment duration of 96 weeks or even longer [71]. However, the HIDIT-2 trials showed no improved off-treatment virological responses with 96 weeks of PEG-IFN compared to the data of the HIDIT-1 trial with 48 weeks of therapy [72]. If patients tolerate PEG-IFN and show a strong decline of HBsAg after 48 weeks, longer treatment may be beneficial to achieve HBsAg loss, which is essential for HDV transmission. Some studies have shown significant rates of HBsAg loss after long-term IFN treatment [73, 74]. Nevertheless, benefits of PEG-IFN therapy need to be balanced with strong side effects and costs. The BEA score predicts the development of liver-related complications in patients with hepatitis D and may help to decide which patients need to be treated urgently [75]. Unfortunately, NUC have no direct influence on HDV replication. However, they can still be useful in HDV-infected patients if HBV DNA is detectable and the hepatitis B requires treatment intervention. Regardless of mono- or co-infection, HBV has to be treated if HBV DNA levels are greater than 2,000 IU/ml or in patients with cirrhosis, if HBV is detectable at all [76]. There are interesting data from patients co-infected with HIV/HBV undergoing long-lasting NUC therapy as part of a highly active antiretroviral therapy. Patients with HIV-HBV-HDV triple infection showed significant HDV RNA reductions in more than half of the patients after mean durations of 5 years of treatment. This may be due to immunological effects. Moreover, long-term tenofovir therapy was associated with an improvement in liver stiffness values in many patients [77]. Even though these data were generated in a rather small patient cohort, based on the extremely beneficial side effect profile, long-term therapy with HBV NUC can be considered in hepatitis D patients with contraindications to IFN and liver cirrhosis.

Combination treatment with PEG-IFN and NUC has been tested in the HIDIT trials [14, 72]. In HIDIT-1, the combination of PEG-IFN and adefovir had a stronger effect on HBsAg decline. However, this was not observed with the combination of PEG-IFN and tenofovir versus PEG-IFN in the HIDIT-2 trial. Therefore, new treatment concepts are urgently required. Lonafarnib, a prenylation inhibitor (interference with host-mediated post-translational changes of proteins), significantly reduced HDV RNA levels in a phase IIa study [78]. Another concept is blocking viral entry with Myrcludex, a preS1 lipopeptide that competes with HBsAg for receptor binding [79]. Although the current developments are still in phase II, approval of drugs may be fast because Europe and the USA have designated hepatitis D as an orphan disease.

Conclusion

Finite PEG-IFN treatment in compensated cirrhosis and NUC treatment in compensated and decompensated cirrhosis can lead to control of HBV replication in the majority of patients with chronic hepatitis B and cirrhosis. Long-term suppression of HBV DNA > 5 years is associated with reversion of fibrosis and early cirrhosis. Patients with decompensated cirrhosis show clinical improvement, and even delisting from liver transplantation is possible. Early treatment initiation and the induction of rapid viral suppression are key for preventing complications, especially in patients with hepatic decompensation. In the case of insufficient virological response, a rescue therapy with another NUC or a combination therapy is often possible. Treatment of patients with cirrhosis also reduces the risk for the development of HCC. However,

patients with cirrhosis remain at a considerable risk for developing HCC despite HBV DNA suppression and require close surveillance. Scores can identify low-risk patients who may not require close monitoring. Hepatitis D is the most progressive form of viral hepatitis. The only effective treatment is PEG-IFN, leading to response rates in 25%. However, treatment is not well tolerated in advanced cirrhosis and late HDV relapse may occur. Thus, new treatment options are urgently required for hepatitis D.

Disclosure Statement

Christoph Höner zu Siederdisen has no conflict of interest. Markus Cornberg has received lecture and consultant fees from Bristol-Myers Squibb, Gilead, Roche Pharma, and Roche Diagnostics as well as grant support from Roche Pharma and Roche Diagnostics.

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