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MINIREVIEWS

Role of antiviral therapy in the natural history of hepatitis B virus-related chronic liver disease

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Abstract

Hepatitis B virus (HBV) infection is a dynamic state of interactions among HBV, hepatocytes, and the host immune system. Natural history studies of chronic hepatitis B (CHB) infection have shown an association between active viral replication and adverse clinical outcomes such as cirrhosis and hepatocellular carcinoma. The goal of therapy for CHB is to improve quality of life and survival by preventing progression of the disease to cirrhosis, decompensation, end-stage liver disease, hepatocellular carcinoma (HCC) and death. This goal can be achieved if HBV replication is suppressed in a sustained manner. The accompanying reduction in histological activity of CHB lessens the risk of cirrhosis and of HCC, particularly in non-cirrhotic patients. However, CHB infection cannot be completely eradicated, due to the persistence of covalently closed circular DNA in the nucleus of infected hepatocytes, which may explain HBV reactivation. Moreover, the integration of the HBV genome into the host genome may favour oncogenesis, development of HCC and may also contribute to HBV reactivation.

Key words: Hepatocellular carcinoma; Nucleos(t)ide analogues; Liver fibrosis; Pegylated interferon; Cirrhosis

Core tip: The goal of therapy for chronic hepatitis B is to improve quality of life and survival by preventing progression of the disease to cirrhosis, decompensation, end-stage liver disease, hepatocellular carcinoma and death. Current therapeutic options do not eradicate hepatitis B virus (HBV) infection, since HBV remains either integrated in the host genome or in the nuclei of hepatocytes as covalently closed circular DNA, a fact that may favour oncogenesis towards the development of hepatocellular carcinoma, and explains HBV reactivation. It is mandatory for clinicians to start viral suppression in patients with active chronic liver disease, particularly in

patients who have already developed advanced hepatic disease.

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INTRODUCTION

Hepatitis B virus (HBV) infection is one of the most serious health problems worldwide. It has been estimated that almost one third of world's population has serological evidence of past or actual exposure to HBV[1,2] and 350-400 million people are chronically infected[1,3,4]. More than 780000 people die every year due to the consequences of hepatitis B[5].

The natural history of HBV infection and of the ensuing liver disease is variable and complex. HBV infection is a dynamic state of interactions among HBV, hepatocytes, and the host's immune system. The resultant hepatic necro-inflammatory response to injury, reflected by alanine aminotransferase elevation or hepatitis activity, may stimulate, during the immune clearance phase, new fibrogenesis that may even lead to progressive fibrosis, causing architectural distortion and cirrhosis. This process may culminate in end-stage liver disease with portal hypertension and may also lead to the development of hepatocellular carcinoma (HCC)[6]. Approximately 15% to 40% of infected patients who develop chronic hepatitis B are expected to progress to cirrhosis and eventually to end-stage liver failure[4,7]. These data have been confirmed in Italy as well, where the HBe-negative/anti-HBe-positive type of chronic B hepatitis (CHB) is predominant, and the 5-year incidence of cirrhosis has been estimated to be 38%[4].

Although it has been generally held true that advanced fibrosis, once present, is static and irreversible, evidence is accumulating to suggest that fibrogenesis is a dynamic process, amenable to arrest or possibly even reversal with removal of the inciting agent[8]. Analogous to the improvement observed with continued abstinence in alcoholic liver disease, with immunosuppression in chronic autoimmune hepatitis, with weight loss in steatohepatitis, and with clearance of hepatitis C virus with interferon and ribavirin, suppression of HBV replication and loss of hepatitis B e antigen (HBeAg) or hepatitis B surface antigen (HBsAg) with antiviral therapy may prevent progressive fibrosis and decompensation.

Recently, concerns have been raised regarding the long-term benefit of HBeAg seroconversion for such patients. Although some observational studies suggest that most Asian patients experience some clinical benefit after HBeAg seroconversion[9,10], this is still an incomplete marker of immune control. HBeAg seroconversion associated with incomplete viral suppression may result in the emergence of precore mutant hepatitis B, with its expected chronic sequelae.

It has been demonstrated that active replication of HBV constitutes the principal trigger for immune clearance, which, in turn, has an impact on clinical outcome[11,12]. Therefore, treatment is primarily aimed at eliminating or permanently suppressing HBV, reducing the activity of hepatitis and slowing down or limiting the progression of hepatic injury. Ultimately, the goals of therapy are prevention or reduction of the risk of developing hepatic decompensation, cirrhosis or HCC, and prolonging survival, through the achievement of sustained viral response and clearance of HBsAg[6].

Several pharmacologic agents including standard interferon (IFN), lamivudine (LAM), pegylated IFN (PEG-IFN), adefovir dipivoxil (ADV), telbivudine (LdT), entecavir (ETV), and tenofovir disoproxil fumarate (TDF) are capable of fulfilling the goals of therapy and have been established as treatment of chronic HBV infection[1].

Moreover, both short- and long-term outcomes of patients with chronic HBV infection are improved, and this will be the focus of this review. Indeed, in this review we will address the following issues: (1) How antiviral therapy may influence fibrosis progression and resolution; (2) The role of the antiviral therapy in patients with decompensated liver disease; and (3) The role of the antiviral therapy in reducing the risk of HCC.

ANTIVIRAL THERAPY, FIBROSIS PROGRESSION AND RESOLUTION

Injury, may it be chronic or acute, elicits a cellular- and cytokine-mediated healing response aimed at limiting or encapsulating injury, which results in fibrosis or scarring of the liver. Damage caused by infections, drugs, metabolic disorders or immunological alterations, and which is maintained in time, promotes the accumulation of significant fibrosis[12].

Hepatic fibrosis is mainly stimulated by hepatic necro-inflammatory activity, and several studies have shown that prolonged antiviral therapy is associated with improvement in liver histology and even reversal of cirrhosis in CHB infection.

Patients who respond to interferon therapy have substantially fewer life-threatening liver complications than non-responders[13], although the evidence of the effect of this therapy on the incidence of hepatocellular carcinoma is less conclusive[14-16]. However, the use of interferon is restricted by costs, side effects, and among patients with advanced liver disease or cirrhosis, due to the risk of liver failure correlated with hepatitis flares. These limitations do not apply to oral nucleos(t)ide anologues-(NUCs), such as Lam and/or ADV, agents that have been used for decades, and the more recent agents ETV, Ldt or TDF. These drugs can produce marked viral

suppression, reduction of hepatic necro-inflammatory activity, histologic improvement of liver fibrosis, and amelioration of liver function, even in patients with decompensation. One of the first pieces of evidence in favor of this statement was established when a reduced risk of liver complications was demonstrated in patients affected by CHB with advanced fibrosis or cirrhosis who were treated with LAM. The magnitude of protection conferred by LAM was substantial, with a reduction of approximately 50% in disease progression during a median period of 32 mo of treatment[17]. Dienstag *et al*[18] confirmed these data showing histological improvement and a reduction in fibrosis score to non-cirrhotic levels in more than 70% of patients treated with LAM with pre-treatment cirrhosis; the proportion was similar regardless of the presence of a tyrosine-methionine-aspartate-aspartate variant. Also noteworthy was the fact that only 2% of non-cirrhotic patients progressed to cirrhosis over this 3.5-year. Sampling error, however, could have perhaps contributed to the observed regression of cirrhosis in these patients, although this is unlikely the case for all patients.

Significant improvement in liver histology was also observed following long-term treatment with ADV. The median change in Knodell necro-inflammation score from the time patients were started on ADV was of 4.5 points at 192 wk and of 5.0 points at 240 wk, and the median change in Ishak fibrosis score was of 1.0 point for both groups. After 48 wk of treatment with adefovir dipivoxil, treatment with adefovir dipivoxil resulted in an increase in the proportion of patients who had improvement of at least 1 point according to Ishak from 35% after 48 wk to 55% and 71% after 192 and 240 wk of treatment, respectively. Of twelve patients with pre-treatment bridging fibrosis or cirrhosis, seven (58%) demonstrated an improvement of at least 2 points in their Ishak fibrosis scores, while a 4-point histologic improvemement was observed in 3 of 4 patients with cirrhosiss[19]. In another study comparing post- and pre-treatment biopsies in patients treated with ADV, significant improvement of hepatic necro-inflammation and fibrosis was observed[20].

Although LAM and ADV have been associated with reversal of fibrosis and cirrhosis, their long-term efficacy has been limited by the emergence of antiviral resistance[18,19]. After treatment with lamivudine for 3 years, 72% of patients with cirrhosis show histologic improvement and a reduction in fibrosis score to non-cirrhotic levels. However, in the same study, 65% of the cohort (41 of 63 patients) developed resistance, including one patient with cirrhosis, who also experienced progression of liver disease at follow-up. Virologic resistance emerged in 20% of the patients treated for 5 years with ADV[18].

For this reason, high genetic barrier treatment regimens have been adopted during the last years, such as ETV, LdT and tumor necrosis factor. Nucleoside-naive, HBeAg(+) and HBeAg(-) patients with cirrhosis/advanced fibrosis at baseline (Ishak fibrosis score, $\geqslant$ 4) and at least 3 years of ETV treatment demonstrate durable suppression of HBV replication, improvement in liver histology, and reversal of fibrosis/cirrhosis[21]. After a median exposure of approximately 6 years to ETV therapy, histological improvement was observed, with a reduction or stability of necroinflammatory score in 96% and reduction of fibrosis in 88% of patients. Most patients (75%) in the cohort who had a F4 baseline HAI score achieved a F3 score by the time of long-term biopsy. No evidence of virological rebound or genotypic resistance to entecavir was observed in this study[22].

In a multicentre study, Marcellin *et al*[23] analyzed the long-term efficacy and safety of of TDF as well as sequential histological data obtained for 5 years in 348 patients, 96 of whom had been diagnosed with cirrhosis at baseline. HBV DNA was undetectable in almost all patients treated with TDF, associated with prevention of fibrosis progression in 96% of the patients overall, and with cirrhosis regression in 74% of patients. Furthermore, a high genetic barrier was demonstrated for TDF, with no evidence for emergence of resistant variants during 5 years of treatment. Although this study provides solid evidence for fibrosis regression, some experts believe that once established, parenchymal destruction and disrupted blood flow in cirrhosis are irreversible. A study showed that hepatic venous pressure gradient (HVPG) was reduced in 18 of 19 cirrhosis patients treated with LAM for 12 mo, whereas portal pressure was reduced at least 20% or below 12 mmHg in 10 of 13 patients in whom baseline HVPG was $\geqslant$ 12 mmHg, suggesting that vascular changes in cirrhosis are reversible in patients with virological and biochemical response[24]. Thus, it seems fairly clear that aside from abatement of HCC incidence demonstrated in the study by Marcellin *et al*[23] cirrhosis is to some degree reversible in patients with sustained HBV suppression and annulled hepatitis activity with NUC treatment.

ANTIVIRAL THERAPY AND DECOMPENSATED LIVER DISEASE

Ascites, hepatic encephalopathy, jaundice, and variceal bleeding represent decompensation milestones in the natural history of an individual cirrhotic patient[25]. In HBV-related cirrhosis, the reported yearly rate of decompensation is 2%-5%[26], and this event can present as part of an acute hepatitis flare or in a more insidious manner[27,28].

Decompensation entails an ominous prognosis, as the 5-year survival rate drops from 84% in compensated cirrhosis to 14%-35% once decompensation has ensued[29,30]. A bulk of evidence indicates that the risk of disease progression is closely linked to a patient's serum HBV DNA level[30-34]. Indeed, a study analyzing 161 patients followed for a median of 6.6 years showed that the risk of hepatic decompensation was 4 times higher in HBV DNA positive patients (13%-18%) *vs* in

HBeAg negative/HBV DNA negative patients (4%, $P = 0.04$)[34]. Persistent HBeAg seropositivity was shown to be significantly ($P = 0.035$) associated with the probability of decompensation in a study analyzing 93 patients with newly developed cirrhosis, and patients in whom HBeAg was persistently positive had a 6 times higher risk of decompensation compared to HBeAg seronegative subjects at entry, during a mean follow-up period of 102 mo[35].

Although it is recommended to commence antiviral treatment as soon as CHB is diagnosed, IFN use, even at low doses, increases the risk of bacterial infections and may provoke an episode of hepatic decompensation. In the era of NUCs, interferon is contraindicated in this patient population[1]. Patients with decompensated cirrhosis may show slow clinical improvement over a period of 3-6 mo under NUCs, after which transplantation may be avoided. In such cases, life-long treatment is recommended[1]. In contrast, some patients with advanced hepatic disease reflected by a high Child-Turcotte-Pugh (CTP) or model of end stage liver disease (MELD) score, may have progressed beyond the point of no return, and may not benefit from medical therapy, thus requiring liver transplantation[36]. In that situation, treatment with NUCs which induces HBV DNA undetectability at transplantation will decrease the risk of HBV recurrence in the graft[37].

LAM has been demonstrated to enact an effective suppression of HBV DNA replication and to significantly ameliorate liver function in decompensated CHB[38,39]. A major drawback of LAM, however, lies in its frequent association with resistant mutants and therefore elevated drug resistance rates[40]. However, the choice of the most adequate antiviral agent at a later disease stage often becomes remarkably difficult, due to the relentless and rapid progression of disease and poor liver function. In the last years, researchers have tried to identify the risk factors for developing decompensation or early signs of non-response to therapy. Post-treatment response was comparatively poor for cases with a cut-off of CTP > 10, MELD > 20, HBV DNA > 7.4 log and total bilirubin > 3.7 mg/dL ($P < 0.05$). Srivastava *et al*[41] showed that a MELD score > 20 was the most potent predictor of mortality among all the factors considered, and that these patients should be considered for orthotopic liver transplantation. In the same paper, the clinical efficacy of antiviral therapy with TDF was proven and showed a rescue activity, achieving more than 90% survival at one year and > 80% survival at 2 years in decompensated Child C cirrhosis[41].

A further issue to discuss regarding antiviral therapy in decompensated cirrhosis due to HBV is the possible occurrence of adverse events. Whereas the safety of LAM has been established, with no reported serious adverse events (SAE), ADV has been reportedly associated with SAE in 4% of patients, including 2% of treated patients with hypophosphatemia in a study analyzing 226 treated patients[42]. In a pooled analysis of two studies, SAE affected 6% of patients treated with ETV[43]. Similar frequency of SAE with ADV and ETV were reported in one prospective study, whereas EDF and ETV were associated with similar SAE rates (4% *vs* 0%, $P = 0.89$) and (7% *vs* 9%, $P = 0.72$), respectively[43,44]. Under ADV treatment, 9% (5%-17%) of patients developed renal insufficiency (defined as an increase in serum creatinine by 0.5 mg/dL over the baseline) occurred in, while this complication was present in 10% (6%-17%) of patients treated with ETV. No cases of renal insufficiency are, on the contrary, reported with LAM. Moreover, renal function improvement (expressed as an increase in estimated glomerular filtration rate from baseline) was significantly greater in patients treated with LdT with respect to patients on LAM therapy (3.3 ± 3.3 mL *vs* 4.3 ± 3.1 mL, $P = 0.02$), according to a prospective randomised controlled trial on LdT and LAM[45]. The frequency of renal insufficiency at 1-year after starting antiviral treatment was reportedly similar between ETV- and TDF-treated patients (5% *vs* 9%, $P = 0.53$) in a different study[44].

ANTIVIRAL THERAPY AND THE RISK OF HCC

The third cause of malignancy-related death in the world, HCC commonly arises in patients with pre-existing cirrhosis or chronic liver disease[46]. Seventy-eight percent of HCCs are related to CHB and chronic hepatitis C infections, occurring approximately in the ratio of 7 to 3, respectively[47]. Different etiologies of liver disease are associated with a greater or lesser risk of HCC, and CHB is the principal underlying cause worldwide[48].

The intricate mechanisms by which the action of the established carcinogen HBV triggers the onset of HCC have not yet been well established. Presumably, the integration of HBV's DNA into the host genome, alongside the direct effect of viral proteins on the hepatocyte are both key components of the direct carcinogenic effect of HBV on hepatocytes. However, possibly the paramount driver of HCC development is the inflammation elicited by HBV, leading to the establishment of cirrhosis, which is almost invariably present in patients with HCC[49].

Not strangely, marked geographical differences in HCC incidence coincide with the prevalence of CHB. While in Scandinavia, the United States, and Canada, incidence is approximately less than 5 cases per 100000, incidence rates peak in central and southeast Asia, with incidence rates that vary from 29 to 99 per 100000[50]. Apart from the solid epidemiological association between the incidence of HCC and the prevalence of CHB, numerous other observations point towards an etiologic link between CHB and the development of HCC[51]. The prevalence of HBsAg is high amongst patients with HCC and HBsAg carriers

have a 98-fold increased relative risk for developing HCC with respect to HBsAg-negative subjects. Further strengthening the evidence in favor of this correlation are the fact that integrated HBV-DNA has been found within neoplastic HCC cells, the recognition that HBV vaccination has been followed by a decrease in HCC incidence, and the observation of an elevated risk of HCC development in animal models of CHB[52].

Preventing disease progression and HCC development in HBV-infected patients is mandatory[53]. As already mentioned, the current therapeutic options for patients with CHB infection may be summarized into treatment with standard or PEG-IFN, a drug with antiviral, immunomodulatory and perhaps antitumoral activities, as well as treatment with oral NUC[1]. In terms of prevention of HCC, IFN therapy, which stimulates immunological check of viral replication, might theoretically represent an advantage regarding prevention of HCC. On the contrary, NUC therapy is likely to represent an advantage over IFN if the direct carcinogenic effect of HBV DNA levels occupies a more preponderant role. Numerous studies and meta-analyses have analyzed the impact of IFN on HCC incidence in patients with CHB, concluding that probably a reduction in the overall incidence of HCC can be obtained with the use of IFN, and that this reduction is more important in patients who maintain a sustained viral reponse. These effect has been more clearly demonstrated in Asian studies *vs* European studies, probably due to the fact that HCC incidence is higher in Asia[15,54-56]. The effect of oral antiviral therapy on HCC incidence, however, has not been clarified.

It has been shown that long-term NUC therapy with initial lamivudine monotherapy is not effective in abolishing the risk of developing HCC risk in HBeAg-negative patients with CHB, particularly in subjects with cirrhosis at baseline. Established independent risk factors for HCC development in CHB patients even after NUC treatment include older age and male gender[57]. Although induction and maintenance of virological suppression appears not to significantly diminish overall incidence of HCC, virological remission on-therapy might be protective in HBeAg-negative patients with CHB but no cirrhosis. On the contrary, as patients with established cirrhosis still stand a high risk of HCC even with an effective antiviral therapy, strict surveillance is warranted[57].

The reduction of the risk of developing HCC is largely dependent upon an agent's capacity to maintain virological remission. In fact, patients in whom a virologic breakthrough is observed, the risk of developing HCC is increased, notwithstanding subsequent suppression of viral replication with rescue therapy. This observation constitutes another element against the use of lamivudine as the first-line treatment of choice, due to its association with high resitance rates during long-term treatment[58].

In a recent randomized controlled trial, Huang *et al*[59] showed that in patients with hepatitis B-related HCC treated with adefovir, antiviral therapy leads to a reduction of late HCC recurrence and significantly improves overall survival after hepatic resection, as opposed to no treatment at all.

In a recent update of the HEPNET Greece cohort study, the authors compared ETV with LAM, showing a lower HCC incidence (of 0.3%, 1.2%, 2.8% *vs* 0.7%, 3.8%, 5.6% at 1, 3, and 5 years, respectively; $P = 0.024$) in the first group. However, in the multivariable Cox regression analysis, the HCC risk was independently associated with older age ($P < 0.001$), male gender ($P = 0.011$) and cirrhosis ($P = 0.025$), but not with the initial antiviral agent[60].

Finally, two recent papers showed that antiviral treatment with ETV did not completely eliminate the risk of developing HCC in patients with cirrhosis[61,62]. These data were confirmed in a recent, large, real-life multicenter United States-based observational cohort study, in which antiviral therapy was associated with a significant decrease in the risk of HCC in patients with chronic HBV infection, but did not eliminate it[47].

In conclusion, it is clear that only with treatments that can completely eradicate the virus from the liver will we be truly able to eliminate the risk of HCC development in patients with HBV-related liver disease.

CONCLUSION

Treatment for CHB infection aims to maximize viral suppression with the objective of controlling liver fibrosis and preventing progression to clinical complications associated with hepatic decompensation and hepatocellular carcinoma. Since necroinflammatory activity is the main stimulator of hepatic fibrosis[12] amidst the intricate pathways leading to HCC development in chronic viral hepatitis[63], it is conceivable that the fibrogenic process will be arrested or even down-graded along with the subsidence of hepatitis activity subsequent to HBV suppression[64]. On the other hand, maintaining undetectable levels of HBV DNA may also increase the rate of HBeAg and HBsAg seroconversion, which are the desired endpoints of CHB therapy[65].

Notwithstanding the solid evidence of viral replication blockade with approved antivirals, the demonstration of advantages in terms of long-term outcomes is more difficult. This is due to the fact that clinical complications develop over decades, and clinical trials with necessarily lengthy follow-up periods are difficult, if not impossible, to perform. In decompensated HBV patients, the waxing frequency of resistance to LAM, ADV and LdT monotherapy, render these three drugs less appropriate. Antiviral therapy using newer NUCs with lower resistance rates such as ETV or TDF could suppress HBV replication, improve liver function in patients with compensated or decompensated cirrhosis, delay or obviate the need for liver transplantation in some patients, and reduce the risk of HBV reactivation.

Finally, current therapeutic options do not eradicate HBV infection and in spite of adequate treatment, the virus remains indefinitely in a latent state, representing

a continuous threat of reactivation and of oncogenic potential leading to HCC development. It is nevertheless mandatory for clinicians to start viral suppression in patients with active chronic liver disease, in particular with those that have already developed advanced hepatic disease, with the aim of avoiding future complications and hopefully reversing at least some degree of hepatic damage.

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