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TOPIC HIGHLIGHT

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Management of chronic hepatitis B in severe liver disease

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Abstract

In the past few decades, chronic hepatitis B (CHB) has evolved from a disease that was untreatable and progressive, to one that can be easily controlled with antiviral therapy. However, patients with severe liver disease still remain difficult to treat despite the availability of highly potent nucleos(t)ide analogs. These include those with underlying cirrhosis, severe flares of CHB, hepatocellular carcinoma (HCC), and for those undergoing liver transplantation. For those with established cirrhosis, antiviral therapy should be considered for all, as unpredictable flares can still occur, which can be fatal for those with advanced chronic liver disease. However, even with effective viral suppression, the development of HCC can still occur. For patients with severe flares of CHB, although the use of antiviral can improve long term outcomes, a significant proportion may still die without liver transplantation. The short term prognosis of these patients is dependent on both the severity of flare and underlying pre-existing liver disease. In patients with decompensated cirrhosis, liver failure secondary to severe flares, or those with HCC, liver transplantation may be curative. After liver transplantation, long term antiviral therapy is required to prevent graft loss from recurrent hepatitis B infection. The use of hepatitis B immune globulin (HBIG) in combination with an oral antiviral agent has been the mainstay of post-transplant antiviral regimen for over a decade. With newer and more potent antiviral agents such as tenofovir and entecavir, use of these agents along with HBIG have demonstrated to be effective in preventing significant recurrence in the long term.

Key words: Antiviral therapy; Cirrhosis; Liver failure; Liver transplantation; Hepatocellular carcinoma

Core tip: This review discusses the treatment of chronic hepatitis B in patients with underlying severe liver disease, including cirrhosis, acute on chronic liver failure, hepatocellular carcinoma, and those undergoing liver transplantation. Despite the availability of highly potent antiviral drugs, these patients are often difficult to manage. The use of currently available antiviral agents is discussed along with its efficacy in these patients with severe hepatitis B liver disease.

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INTRODUCTION

With an estimated 400 million people worldwide infected with the hepatitis B virus (HBV), chronic hepatitis B (CHB) continues to be a major global health problem. Up to 40% of patients infected with CHB may develop liver complications, including cirrhosis, liver decompensation, and hepatocellular carcinoma (HCC)[1]. In a recent study of 6689 CHB patients, HBV was the cause of death in over 40%, and the rate was similar between non-Asians and Asia-Pacific Islander origin[2]. Not until the recent decade, CHB was largely a progressive and untreatable disease. The major milestone in CHB manage-

ment was the approval of the first nucleoside/nucleotide analogue (NA), lamivudine (LAM) in 1998. However, LAM was associated with high rates of resistance[3]. Since then, four other NAs have been approved for the treatment of CHB, namely adefovir (ADV), entecavir (ETV), telbivudine, and tenofovir (TDF). All NAs are effective in achieving the short term goals of HBV DNA suppression and normalization of liver parenchymal enzymes[4-11]. The key difference between the NAs pertain to their varying barriers to resistance[12]. Through the effects of viral suppression, long-term treatment with NAs can reduce and prevent the development of cirrhosis and reduce the development of HCC[13-17]. However, a significant proportion of HBV carriers remain untreated for various reasons. As CHB is largely asymptomatic, HBV carriage is unlikely to be apparent unless it is screened. Once diagnosed, treatment may not be instituted because of ineligibility according to current treatment guidelines, cost, compliance to follow-up, and patient's own decision. It is therefore not surprising that a significant proportion of HBV carriers can present for the first time with advanced liver disease.

MANAGEMENT OF CIRRHOSIS

In patients with advanced fibrosis and established cirrhosis, long term therapy with NAs can lead to regression of fibrosis and even cirrhotic changes[18-22]. However, in advanced stages of cirrhosis, when the liver is already contracted with gross lobular architectural distortions and portal hypertension, the changes are likely to be irreversible. Although antiviral therapy should ideally have been started prior to the onset of progressive liver fibrosis, there are major reasons for treating patients with established cirrhosis. The goals of treatment for this population are to prevent further liver injury and progressive liver damage leading to decompensation, to improve liver function, and to decrease the risk of HCC development and ultimately, to reduce mortality.

Ideally, all CHB patients with cirrhosis and detectable viral load should be considered for treatment. However, there are differences in the criteria for starting antiviral therapy for HBV cirrhosis between the major regional treatment guidelines. The European Association for the Study of the Liver guidelines recommend that treatment should be started using a drug with low resistance profile irrespective of the level of alanine aminotransferase (ALT) as this may be normal in advanced liver disease[23]. The American Association for the Study of Liver Diseases (AASLD) guidelines suggest that treatment for compensated patients should only be started when ALT > × 2 upper limit of normal, or if the HBV DNA level is elevated (> 2000 IU/mL) with elevated ALT[24]. For patients with decompensated cirrhosis, treatment should be promptly initiated with a NA that can rapidly suppress viral load with a low risk of drug resistance. The Asia Pacific Association for the Study of the Liver (APASL) guidelines recommend treatment for those with HBV DNA levels ⩾ 2000 IU/mL with compensated cirrhosis[25]. However, spontaneous flares of hepatitis can occur at any time, and in patients with cirrhosis (even if compensated), these episodes may lead to decompensation, increasing chance of death or the need for liver transplantation (LT). Therefore, all HBV cirrhotic patients who remain hepatitis B surface antigen (HBsAg) positive should be considered for antiviral therapy.

The duration of therapy for patients with cirrhosis should be long-term. For compensated cirrhosis, the AASLD guidelines recommend that treatment can be stopped in hepatitis B e antigen (HBeAg)-positive patients if they undergo HBeAg seroconversion together with at least 6 mo of consolidation therapy, or in the event of HBsAg seroconversion for HBeAg-negative patients[24]. However, the risk of virological rebound in patients with treatment-induced HBeAg seroconversion after cessation of antiviral therapy has been shown to be significantly high[26]. As virological rebound and subsequent flare after discontinuing treatment may result in decompensation in cirrhotic patients, it would be prudent to consider long-term maintenance antiviral therapy. For decompensated patients, life-long treatment is recommended.

The long term benefits of oral antiviral therapy in cirrhotic CHB patients was established in a multicenter randomized placebo-controlled trial of 651 patients using LAM, showing significant reduction in overall disease progression, lower rate of Child-Pugh score increase, and a reduction in the development of HCC[13]. Subsequent non-placebo trials have demonstrated the efficacy of newer NAs in decompensated liver disease. A randomized study comparing ETV and ADV demonstrated superior viral suppression with ETV, with similar improvements in Child-Pugh scores[27]. A randomized study comparing TDF (n = 45), TDF + emtricitabine (n = 45), and ETV (n = 22) showed similar efficacy in HBV DNA suppression, and improvement in Child-Pugh and MELD scores[28]. In fact, an earlier study using LAM showed a biphasic survival pattern, with a high mortality rate within the first 6 mo due to liver failure in patients with decompensated cirrhosis[29]. Factors associated with early mortality included bilirubin, creatinine, and HBV DNA levels. For those surviving beyond 6 mo, the long term survival was excellent (88% at 3 years). The importance of HBV DNA suppression in decompensated cirrhotic patients was highlighted in a randomized placebo-controlled trial using TDF in 27 patients[30]. Those patients treated with TDF had significant reduction in HBV DNA levels with improvements in Child-Pugh and MELD scores, and reduction in mortality. A greater than 2 log reduction in HBV DNA levels at week 2 was found to be an independent predictor of survival.

It is likely that the short term survival is independent of the type of antiviral therapy, and non-head to head comparison studies have shown similar 1-year survival rates of 84%-93% between the five currently approved NAs in decompensated CHB cirrhosis[29,31,32]. As previ-

ously mentioned, virtually all patients with cirrhosis who are commenced on antiviral therapy will require life-long treatment. Therefore, NAs with a high barrier to resistance should be used to minimize the risk of virological breakthrough and subsequent flares, as this can often lead to disastrous consequences in patients with established cirrhosis[33-38]. A recent meta-analysis comparing ETV and LAM showed similar reduction in mortality, with better virological response and lower rate of resistance observed in those treated with ETV[39].

In patients with severe liver disease, there should be heightened vigilance to ensure that any adverse effects from medication use are minimized. There have been cases of severe lactic acidosis occurring with the use of ETV in patients with impaired liver function[40]. These patients all had higher MELD scores of > 18 with impaired creatinine clearance. Therefore, patients with renal impairment should have their antiviral dose adjusted accordingly. In the randomized trials of ETV in decompensated cirrhosis, no lactic acidosis was reported[27,28].

ACUTE FLARE OF CHB

Acute flare of CHB can occur in both treatment-naïve patients and those already on antiviral therapy. In the former setting, loss of immunotolerance in HBeAg-positive patients may result in acute flares. For those who are HBeAg-negative, ongoing viral replication can still occur, leading also to recurrent flares. For treated patients, acute flares can occur with cessation of therapy or non-compliance, and also with the development of drug resistant mutations. In severe cases, acute flares can lead to acute on chronic liver failure (AOCLF). The APASL consensus has defined AOCLF as an acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 wk by ascites and/or encephalopathy in patients with existing chronic liver disease[41]. The development of AOCLF depends on 2 key factors, the severity of the acute insult and the degree of underlying chronic liver disease. Liver failure can occur with a moderate flare with underlying cirrhosis, or with a severe flare in non-cirrhotic patients.

As discussed previously, the biphasic pattern of survival means that a significant proportion will succumb within the first few mo of presentation even with the commencement of antiviral therapy. The use of molecular adsorbent recirculating system (MARS) can decrease plasma concentration of bilirubin, creatinine, and ammonia in AOCLF. Initial small randomized trials of patients with AOCLF suggested that using albumin dialysis may improve survival[42-44]. However, in a recent multicenter trial of 189 AOCLF patients randomized to receive MARS (n = 95) *vs* standard (n = 94) therapy, there was no difference in the 28 d transplant-free survival (60% *vs* 59.2% respectively, P = 0.88) and in the 90-d transplant-free survival (44.7% *vs* 43.7% respectively, P = 0.97)[45]. Thus although MARS therapy is safe in this group of patients, there does not appear to be any survival benefit.

Therefore, for those patients not responding to antiviral therapy, LT remains the only curative option. For those with evidence of liver decompensation, early referral to a LT center is recommended. There is currently no consensus on whom and when to transplant, and the most widely adopted criteria is the King's criteria for acute liver failure. However, many of these patients have underlying chronic liver disease and may not fulfil the criteria for acute liver failure. In addition, patients with AOCLF often evolved into a chronic state, without fulfilling the King's criteria, but remain decompensated without transplantation. There are studies showing that MELD score on presentation could be used to predict mortality from AOCLF. For patients with MELD score greater than 30, the short-term mortality can be as high as 92% even when NAs are given[46,47]. These patients should be urgently considered for LT. For those with intermediate MELD score *e.g.*, 20-30, the short-term mortality is around 44%-50%. Monitoring other prognostic parameters is therefore required and LT may also be required. These parameters include prothrombin time, INR, creatinine, sodium, the presence of hepatic encephalopathy, the presence of cirrhosis, hepatorenal syndrome, HBeAg status, and albumin[48-51]. In the absence of the definite criteria for AOCLF, clinical judgment is often made on factors such as the presence of hepatic encephalopathy, degree of liver dysfunction including the level of jaundice and coagulopathy, the presence of multiorgan involvement, and the use of imaging to determine the presence of underlying cirrhosis, portal hypertension and dynamic changes in liver size with serial scanning.

The outcome after LT for AOCLF is excellent, and is similar to those achieved by LT for other liver conditions. In a study of 50 patients with acute flare of CHB and 99 cirrhotic patients with acute decompensation, the 5-year survival rate was 93.2% and 90.5% respectively[52].

HEPATOCELLULAR CARCINOMA

It is well known that HBV replication is an important contributing factor for the development of HCC[53]. Antiviral therapy remains the cornerstone in reducing the incidence in HCC[54]. Studies using LAM demonstrate a reduction in HCC development in both cirrhotic and non-cirrhotic patients, although the benefit is diminished by the development of drug resistance[3,13,55]. Failure to remain in virological remission is a risk factor for HCC[56]. A case control study showed a lower cumulative 5-year HCC incidence in patients treated with ETV compared to the control group (3.7% *vs* 13.7% respectively, P < 0.001), with a lower risk of HCC in the ETV group (HR = 0.37, 95%CI: 0.15-0.91, P = 0.30)[16]. An analysis of 2671 CHB patients, antiviral therapy was associated with a lower risk of HCC compared with non-treated patients (adjusted HR = 0.39, 95%CI: 0.27-0.56, P < 0.001)[57]. Several meta-analyses/systematic reviews have also shown the benefits of antiviral therapy in reducing the rate of HCC development[58-61]. A recent systematic review and

meta-analysis however was less clear on the benefits of antiviral therapy in preventing HCC and mortality[62]. Unfortunately, antiviral therapy will not completely remove the risk of HCC, especially for those with established cirrhosis where the liver is already prone to carcinogenesis even without viral replication[56]. Therefore, close follow-up and stringent surveillance for the development of HCC is essential for all cirrhotic patients.

Once HCC develops, treatment for HBV will depend on the stage of disease and the treatment undertaken. Ideally, all patients should be on antiviral therapy as the majority will have underlying cirrhosis. Even for non-cirrhotic patients, the fact that HCC has developed shows that the virus itself has an important role in hepatocarcinogenesis. For non-surgical patients, a high viral load prior to chemotherapy results in higher rates of severe hepatitis during chemotherapy[63]. The APASL guidelines recommend that antiviral treatment should be commenced in all HCC patients with HBV DNA > 2000 IU/mL before and/or after curative therapy, and treatment should be started preemptively for all patients undergoing transarterial chemo-embolization (TACE)[25]. Longer survival has been shown in patients receiving TACE with the additional of antiviral therapy[64]. For those with advance stage HCC where survival is limited, resistance becomes less of an issue, and a more cost-effective approach may be recommended[65].

For the overwhelming majority of patients with HCC, surgical removal of the tumor by resection or LT is the only curative option; the latter will be discussed in a subsequent section. Antiviral therapy is important for patients undergoing resection as the hepatic reserves will be limited and compromised in the post-operative period. Therefore, flares of hepatitis may lead to decompensation for untreated patients[66]. Surgery and anesthesia may also impart a state of immunosuppression in the early post-operative period, thereby increasing the risk of HBV reactivation[67]. A high pre-operative viral load has been associated with worse overall and recurrence-free survivals after curative resection[68]. There is also the potential increased risk of recurrent HCC due to the process of necrosis and regeneration of remaining hepatocytes, which may induce DNA mutations and instability. Up-regulation of adhesion molecules on cells lining sinusoids may increase the risk of distant metastasis[69].

Viral load and hepatic inflammatory activity have been associated with late recurrences after HCC resection[70]. A cohort of 72 resected patients with HBV-related HCC showed that the absence of antiviral treatment was a risk in tumor recurrence[71]. An HBV DNA of > 2000 IU/mL at the time of resection was a significant risk factor (RR = 22.3, 95%CI: 3.3-150.5, $P = 0.001$). In a nationwide cohort study from Taiwan of 4051 untreated *vs* 518 NA-treated CHB patients with resected HCC, even though there was a higher rate of cirrhosis in the latter (38.7% *vs* 48.6% respectively, $P < 0.001$), the risk of HCC recurrence was lower in the NA-treated patients (43.6% *vs* 20.5% respectively, $P < 0.001$)[72]. NA use was independently associated with a significantly lower HCC recurrence risk (HR = 0.67, 95%CI: 0.55-0.81, $P < 0.001$).

Therefore, antiviral therapy plays an important role in preventing the development of HCC, but also in the recurrence of HCC after curative resection. A meta-analysis also demonstrated the beneficial effects of antiviral therapy with regards to HCC recurrence (OR = 0.59, 95%CI: 0.35-0.97, $P = 0.04$), and liver-related mortality (OR = 0.13, 95%CI: 0.02-0.69, $P = 0.02$)[73]. Another recent meta-analyses including 20 studies demonstrated that the presence of high viral load significantly increased overall HCC recurrence risk after curative therapy, whereas antiviral therapy had potential beneficial effects in preventing recurrence[74].

LIVER TRANSPLANTATION

Indications for LT in CHB include severe flares, chronic decompensation, and the development of HCC. The goals of therapy for these patients have been discussed in detail for patients with acute flares, decompensated cirrhosis, and also for patients with HCC[75]. There is also evidence to suggest that antiviral therapy before LT may prevent HBV recurrence after LT by reducing the level of viremia to extremely low levels[76-78]. After LT, the primary goal of antiviral therapy is to prevent HBV recurrence and to prevent graft loss. Prior to the availability of effective HBV prophylaxis in the 1980s, LT for CHB was a relative contraindication. High rates of graft re-infection leading to severe flares and loss of graft occurred in the absence of antiviral therapy. The use of hepatitis B immune globulin (HBIG) after LT was the first major milestone in the prevention of post-transplant HBV recurrence. HBIG monotherapy reduced HBV recurrence by a rate of approximately 70%[79]. As it is a type of passive immunization, the effects are immediate and transient, resulting in the need for frequent antibody titer monitoring and parental injection. The second milestone was the approval of LAM for the treatment of CHB. Although LAM monotherapy is effective in preventing 60%-95% of HBV recurrence, a major disadvantage is the high rate of drug resistance[80]. By combining HBIG with LAM, over 95% of HBV recurrence can be prevented. This combination has been the mainstay of therapy for most LT centers worldwide for the past few decades. The cost of HBIG therapy can be reduced through the use of lower doses which have shown to be equally efficacious[81].

With the availability of highly potent NAs with low drug resistance rates, recent studies have shown that an HBIG-free regimen can be adopted. An early small-scaled study demonstrated that HBIG can be safely withdrawn with the addition of ADV together with LAM without an increase risk in virological relapse[82]. A recent study also demonstrated no HBV recurrence at 96 wk for patients treated with emtricitabine + TDF + HBIG, with cessation of HBIG after 6 mo post LT[83]. A completely HBIG-free regimen in a cohort of CHB patients using

ETV monotherapy, has been reported, showing no episodes of HBV flares or graft loss secondary to recurrent HBV infection[84]. The combination of LAM + ADV without HBIG has also been shown to be effective[85]. A recent large long-term cohort study of 362 CHB post-LT patients receiving only NAs without HBIG showed that at year 8 after LT, 98% had undetectable HBV DNA. Moreover, the survival was excellent at 83% at 8 years, with no mortality related to HBV recurrence[86]. This clearly shows that an HBIG-free regimen is safe and effective, and increasing studies have also demonstrated the efficacy of this therapeutic approach[87-93].

However, HBIG remains part of the antiviral prophylaxis in many transplant centers. It has to be said that the use of HBIG is likely to result in a higher rate of HBsAg negativity due to the fact that the passive anti-HBs antibodies will bind with HBsAg, leading to a further reduction in detection rate when compared with HBIG-free protocols. However, this does not signify eradication of HBV as cessation of prophylaxis is likely to result in reactivation. Therefore, life-long antiviral therapy is currently the standard of care after LT for CHB.

CONCLUSION

In patients with CHB, complications of liver disease can occur in around 40% of patients, including cirrhosis and HCC. The use of interferon-based therapy is largely contra-indicated for those with severe liver disease; therefore treatment is restricted to the use of NAs. After curative resection, adjuvant interferon therapy also fails to demonstrate any reduction in recurrence of HCC after curative resection[94]. Although there are slight variations between the different major regional treatment guidelines, general recommendations can be made with the use of the current available NAs in the treatment of patients with cirrhosis, AOCLF, HCC, and after LT. The use of drugs with high antiviral potency and high barrier to resistance is recommended (ETV or TDF), to minimize the development of resistance, virological breakthrough and biochemical flare. Earlier drugs with low antiviral potency or low barrier to resistance, such as LAM or ADV, should not be used. The duration of treatment is life-long for the overwhelming majority, with cessation of therapy perhaps only possible for those with HBsAg seroconversion. Ongoing surveillance for HCC is an essential component of management for cirrhotic patients. In patients with HCC, antiviral therapy is recommended to preserve liver function in the non-tumor liver, especially for those undergoing liver resection and loco-regional ablative therapy. For those with AOCLF and those with decompensated cirrhosis, early consideration for transplantation is recommended if available. Although antiviral therapy is effective for AOCLF, a significant proportion will still succumb. Life-long prophylaxis is currently the standard of care for patients after transplant. With the newer NAs, a regimen without the use of HBIG has been shown to be effective with excellent long-term outcome.

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