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Review

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Hepatitis B virus-related decompensated liver cirrhosis: Benefits of antiviral therapy

Cheng-Yuan Peng[1,2], Rong-Nan Chien[3], Yun-Fan Liaw[4,*]

[1]*School of Medicine, China Medical University, Taichung, Taiwan;* [2]*Division of Hepatogastroenterology, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan;* [3]*Liver Research Unit, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Keelung, Taiwan;* [4]*Liver Research Unit, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taipei, Taiwan*

Summary

Following development of liver cirrhosis in patients with chronic hepatitis B, liver disease may continue to progress and decompensation or hepatocellular carcinoma (HCC) may occur, especially in those with active viral replication. Decompensation may manifest with jaundice, ascites, variceal bleeding or hepatic encephalopathy. Earlier studies have shown that the prognosis of decompensated cirrhosis is usually poor with a 5-year survival rate at 14–35% under conventional standard of care. The approval of oral antiviral agents has greatly improved the prognosis, as demonstrated in several cohort studies and randomized clinical trials involving therapy with lamivudine, adefovir dipivoxil, entecavir, telbivudine, or tenofovir disoproxil fumarate. Oral antiviral agents are effective in restoring liver function and improving survival in patients with decompensated cirrhosis especially if therapy is initiated early enough. These agents are generally well tolerated without significant side effects. However, their preventive effect in HCC development has yet to be convincingly demonstrated. Given their known resistance profiles, entecavir and tenofovir should be considered as the first-line therapy for patients with HBV-related decompensated cirrhosis.

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Introduction

Chronic hepatitis B virus (HBV) infection is a serious health problem because of its worldwide distribution and its potential adverse sequelae, including cirrhosis and hepatocellular carcinoma (HCC) [1,2]. It was estimated that more than 200,000 and 300,000 chronic HBV carriers worldwide die of liver cirrhosis and HCC, respectively, each year [3]. Since HBV replication, reflected in the presence of serum hepatitis B e antigen (HBeAg) and/or HBV DNA ⩾2000 IU/ml, may persist after the development of cirrhosis [4], liver disease may continue to progress and hepatic decompensation or HCC may occur. In recent years, remarkable advances have been achieved in the understanding of the natural course after the development of cirrhosis, in the general management of its complications and in the antiviral treatment of this patient population. This review summarizes the advances in general and the benefits of current antiviral therapy in particular.

Keywords: Antiviral therapy; Hepatitis flare; Hepatocellular carcinoma; Nucleos(t)ide analogues; Entecavir; Tenofovir disoproxil fumarate.

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* Corresponding author. Address: Liver Research Unit, Chang Gung University and Memorial Hospital, 199, Tung Hwa North Road, Taipei 105, Taiwan. Tel.: +886 3 3281200x8120; fax: +886 3 3282824.

E-mail address: liveryfl@gmail.com (Y.-F. Liaw).

Abbreviations: ADV, adefovir dipivoxil; CHB, chronic hepatitis B; CTP, Child–Turcotte–Pugh; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HE, hepatic encephalopathy; HIV, human immunodeficiency virus; HRS, hepatorenal syndrome; LAM, lamivudine; LdT, telbivudine; MELD, model for end stage liver disease; Nuc, nucleos(t)ide analogue; SBP, spontaneous bacterial peritonitis; TDF, tenofovir disoproxil fumarate.

Natural course after the development of cirrhosis

A substantial proportion of patients with cirrhosis have active HBV replication. A prospective study on cirrhosis detected during long-term follow-up of patients with chronic hepatitis B (CHB) in Taiwan showed that 30% of the 93 patients were seropositive for HBeAg and 73% had a serum HBV DNA level >10,000 copies/ml (2000 IU/ml) at the time of cirrhosis detection with a mean age of 43.6 (24–69) years. During a follow-up period of 12–246 (median 97, mean 102 ± 60) months, hepatitis flare, HBeAg seroconversion, and hepatitis B surface antigen (HBsAg) loss occurred in 32 (34%) of 93, 15 (54%) of 28, and 12 (13%) of 93 patients, respectively; and hepatic decompensation, HCC, and mortality occurred in 12 (13%), 21 (23%), and 11 (12%) patients, respectively [4]. Two earlier studies from Europe showed that 35%-55% of patients with compensated cirrhosis were HBeAg positive [5,6] and 48% of patients in one study were HBV DNA positive (by hybridization) at presentation [6]. HBeAg positivity at presentation was associated with a worse survival and HBeAg or HBV DNA seroclearance during follow-up was associated with a better survival. The cumulative probability of survival at 5 years was 84% for both studies [5,6]. These studies suggest that at least 30–70% of the patients still have active viral replication at presentation of compensated cirrhosis, and that active viral replication is associated with continued liver disease progression and decreased survival over time. By contrast, concurrent hepatitis C virus (HCV) or hepatitis D virus (HDV) infection in HBV-related

cirrhosis may suppress HBV replication despite continuing liver disease progression [7].

Development of HCC

Cirrhosis is the most important risk factor for HCC development. Risk factors for developing HCC in HBV-related cirrhosis include older age, male gender, severity of liver disease, active viral replication during follow-up, viral genotype, viral mutants, concurrent HCV or HDV infection, alcohol intake, and aflatoxin exposure [8]. The risk of HCC in cirrhotic patients is higher in East Asia than in the West, possibly because of earlier acquisition of HBV infection and a longer duration of disease. Combining all data from published studies, the 5-year cumulative incidence of HCC in cirrhotic patients was reported to be 17% in East Asia and 10% in the West [7]. A population-based cohort study in Taiwan showed that baseline HBV DNA level >10^4 copies/ml was the strongest independent predictor of HCC at a dose-dependent manner after adjustment for age, sex, smoking, alcohol, HBeAg status, and serum ALT level. However, the predictive role of baseline HBV DNA level in HCC development in the subgroup of patients with cirrhosis was not reported [9]. Several clinical studies in patients with cirrhosis showed no significant correlation between HBV DNA level or HBeAg status and the development of HCC [4,10,11]. However, two studies from Japan showed a significant correlation between baseline HBV DNA level and the risk of HCC and that persistence of high HBV DNA level (>5000 copies/ml) during follow-up was associated with an increased risk of HCC development [12,13]. The Taiwan study showed that persistent HBeAg seropositivity was related to HCC development with marginal significance ($p = 0.062$) in multivariate analysis [4]. The controversies on the role of baseline viral load and persistence of viral replication in the development of HCC in patients with cirrhosis require further study.

Development of hepatic decompensation

Decompensation usually presents with at least one episode of ascites, jaundice, hepatic encephalopathy (HE) or variceal bleeding [5,10]. Several cohort studies have shown that 2–5% of patients with HBV-related compensated cirrhosis developed decompensation each year [4,10,11]. This can develop insidiously or as a complication of acute hepatitis flare [14,15]. The latter was demonstrated in a study showing that hepatic decompensation developed in 14% of cirrhotic patients who experienced hepatitis flares [14]. These two modes of hepatic decompensation have not been clearly differentiated and compared in terms of prognosis. One study in 161 patients showed that the risk of hepatic decompensation during a median follow-up period of 6.6 years was 4-fold higher in HBV DNA positive patients (13–18%) than in HBeAg negative/HBV DNA negative patients (4%, $p = 0.04$) at entry [11]. Another study of 93 newly developed cirrhotic patients showed that persistent HBeAg seropositivity was significantly ($p = 0.035$) associated with the development of decompensation and the risk of hepatic decompensation during a mean follow-up period of 102 months was 6-fold higher in persistently HBeAg positive patients than in patients who were seronegative for HBeAg at entry [4]. These data suggest that seropositivity for HBeAg or HBV DNA at presentation or HBeAg persistence, reflecting active HBV replication, in compensated cirrhosis is an important factor contributing to further disease progression.

Other than active HBV replication, other hepatitis virus(es) superinfections in HBV-related cirrhotic patients may increase the development of decompensation during the acute phase [16,17] and could be a cause of decompensation during the chronic phase of HCV or HDV superinfection [7,17].

Natural history after the first episode of hepatic decompensation

Earlier European studies showed that the first episode of decompensation most commonly presented with ascites and the prognosis after the development of decompensation was poor, with a 5-year survival rate of 14–35% [5,10,11]. The presenting features of decompensated cirrhosis, its subsequent survival and prognostic indicators were investigated in two Asian studies. A retrospective cohort study involved 96 patients with a median follow-up duration of 3.5 years following the onset of hepatic decompensation. At presentation, the mean age was 54 years and 24% of the patients were HBeAg seropositive. The presenting features were ascites (70%), variceal bleeding (34.3%), jaundice (26%), spontaneous bacterial peritonitis (SBP, 7.3%), and HE (5.2%). Twenty-nine percent of the patients had more than one feature of decompensation. HCC developed in 24 (25%) patients during a median duration of 3 (0.45–7.9) years. The overall 2-year survival rate was 80% after the onset of decompensation. The causes of death were hepatic failure (52.9%), HCC (29.4%), variceal bleeding (5.9%), and SBP (4.4%). HE and hypoalbuminemia ($\leqslant$2.8 g/dl) were significant prognostic factors. HBeAg status was not a significant prognostic factor although serum HBV DNA level was not examined in this study [18]. Another retrospective–prospective cohort study enrolled 102 untreated decompensated cirrhotics with a mean follow-up duration of 46 months. The mean age was 46 years and 28% of the patients were HBeAg seropositive. The presenting features were ascites (63%), variceal bleeding (37%), and HCC (10%). HCC developed in 3% during follow-up. During a median follow-up duration of 13 months, 22 patients died and Kaplan–Meier survival analysis showed a 5-year survival rate of 19%. The causes of death were hepatorenal syndrome (HRS, 32%), variceal bleeding (23%), HCC (28%), liver failure (9%), and HE (9%). Initial decompensation with ascites and development of sepsis with features of systemic inflammatory response were independent predictors of death [19]. Three of the above five studies examined the impact of the HBeAg status on the survival but did not find significant association [5,18,19]. None of the studies assessed the predictive role of baseline HBV DNA level in patient survival. Therefore, the prognostic significance of HBV viremia at the decompensated stage of cirrhosis remains to be studied.

The natural history of HBV-related cirrhosis and decompensated cirrhosis is summarized in Fig. 1 and Table 1.

General management of patients with decompensated cirrhosis

Upon detection or presentation, patients need to be evaluated carefully. The evaluations include liver function status, complete blood cell counts, cause(s) of decompensation (HBV, HCV or HDV), the presence and degree of varices, ascites with or without peritonitis, and HE. The Child–Turcotte–Pugh (CTP) score and

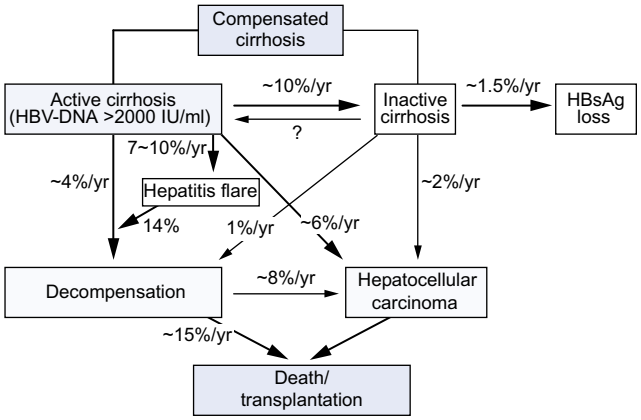

Fig. 1. Natural history of hepatitis B virus (HBV)-related cirrhosis. /yr, per year.

Model for End Stage Liver Disease (MELD) score are the two liver-specific scoring systems that have been used to assess disease severity in patients with cirrhosis. The CTP score was originally developed to predict post-operative mortality in bleeding alcoholic cirrhotics undergoing portal-systemic shunt surgery [20]. Although it predicts 1-year survival and post-surgical risks of complications, it does not predict short-term mortality [21]. The MELD score was initially developed to predict short-term mortality in patients undergoing transjugular intrahepatic portosystemic shunt [22]. It was later used to predict 3-month mortality in patients with cirrhosis, irrespective of cause, and has been adopted to prioritize organ allocation for liver transplantation in the United States since 2002 [23,24]. A major feature of the MELD scoring system is the inclusion of renal function in the model. Renal dysfunction commonly occurs during the course of disease progression in cirrhosis and has been shown to have a prognostic impact on survival [25].

Standard of care in patients with decompensation according to their presentations, including control of ascites, bleeding, infection or encephalopathy, should be instituted promptly and adequately [26]. Surveillance of HCC and timely consultation or referral for liver transplantation is also mandatory [27,28]. For decompensation due to other hepatitis viral superinfections, anti-HBV therapy is useless and liver transplantation is the more immediate option.

Antiviral drug therapy

Antiviral therapy should be initiated as soon as the diagnosis has been established. The immediate goal of antiviral therapy is to improve hepatic dysfunction and rescue the patients from mor-

Table 1. Natural history of HBV-related decompensated cirrhosis.

Study, [Ref.]	de Jongh *et al.*, [5]	Fattovich *et al.*, [10]	Fattovich *et al.*, [11]	Hui *et al.*, [18]	Das *et al.*, [19]
Number of patients	21	88	33	96	102
Age (yr)	46[a]	n.r.	n.r.	54[b]	46[b]
Follow-up period (yr)	4.3[b]	n.r.	n.r.	3.5[a]	1.1[a]
Presenting features					
Ascites, (%)	62	30	49	70	63
Variceal bleeding, (%)	n.r.	8	9	34.3	37
Jaundice, (%)	48	17	12	26	8
SBP, (%)	n.r.	n.r.	n.r.	7.3	n.r.
HE, (%)	19	n.r.	0	5.2	0
HCC, (%)	n.r.	0	0	0	10
More than one feature, (%)	n.r.	47	30	29	n.r.
HBeAg/HBV DNA positive, (%)	52/n.r.	n.r.	n.r.	24/n.r.	28/n.r.
HCC development , (%)	n.r.	n.r.	n.r.	25	3
Survival					
1-year, (%)	70	58	71	90	n.r.
3-year, (%)	35	40	40	80[c]	n.r.
5-year, (%)	14	35	28	n.r.	19
Cause of death					
Hepatic failure, (%)	n.r.	n.r.	64	52.9	9
HCC, (%)	n.r.	n.r.	n.r.	29.4	28
Prognostic factors	n.r.	n.r.	n.r.	HE, Alb ≤2.8 g/dl	ascites presentation, sepsis with SIRS

Alb, albumin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; n.r., not reported; SBP, spontaneous bacterial peritonitis; SIRS, systemic inflammatory response syndrome.
[a]Median.
[b]Mean.
[c]Two-year survival rate.

tality. The clinical improvement in some wait-listed patients with antiviral therapy can result in their withdrawal from the transplant list [27–31].

The use of interferon alfa in patients with HBV-related decompensated cirrhosis can precipitate clinical decompensation and increase the risk of bacterial infection, even with low doses. In the era of nucleos(t)ide analogue (Nuc), interferon is contraindicated in this patient population.

Currently, lamivudine (LAM), adefovir dipivoxil (ADV), entecavir (ETV), telbivudine (LdT), and tenofovir disoproxil fumarate (TDF) have been approved for CHB therapy. All of these Nucs are competitive inhibitors of the HBV DNA polymerase via competition with the incorporation of the natural endogenous intracellular nucleotides in nascent HBV DNA and cause DNA chain termination. All of these Nucs have activities conferring biochemical, virological, and serological improvement in CHB patients [29–31]. They can also retard the progression of fibrosis and reverse fibrosis and cirrhosis [32–34]. Long-term therapy may also prevent hepatic decompensation in patients with advanced fibrosis and cirrhosis [35]. More importantly, it has demonstrated efficacy in rescuing patients with decompensated CHB since year 2000 [15]. The number of candidates on the waiting list of liver transplantation for HBV-related decompensated liver disease in the United States has decreased significantly since then [36]. LAM therapy has the longest history of extensive evaluation. The efficacy and safety of these drugs are summarized below.

Lamivudine

LAM is an L-nucleoside analogue and is the first oral agent licensed for treatment of CHB. It is generally safe and well tolerated. Earlier studies involving a relatively small number (13–35) of patients with decompensated cirrhosis consistently showed significant increase in serum albumin, decrease in serum bilirubin and decrease in CTP score as compared to baseline [37–40]. In decompensated wait-listed patients for liver transplantation, a study showed that LAM therapy improved biochemical and virological profiles and survival in non-transplanted patients, and also protected against HBV reinfection with improved survival in transplanted patients [41]. Another study showed that liver transplantation was performed in a significantly smaller proportion of LAM-treated patients than in controls (35% *vs.* 74%, $p = 0.04$), and time to death or liver transplantation was also significantly longer in LAM-treated patients [42].

The severity of liver disease at the time of LAM treatment initiation may have an impact on the time it takes for liver functions to recover. A small study showed that patients of Child class B needed shorter time to achieve a 2-point reduction in CTP score (5.9 *vs.* 14 months, $p < 0.001$) and to gain a 0.5 g/dl increment in albumin (5.8 *vs.* 14 months) than patients of Child class C [43]. These results suggest that patients with decompensated cirrhosis should receive antiviral therapy as early as possible to allow a better chance of functional recovery.

Not all patients with decompensated cirrhosis survived LAM treatment; it is thus important to identify factors predictive of early death following the institution of LAM therapy to allow timely intervention of liver transplantation to prevent mortality. A prospective multicenter study involving LAM therapy in 154 North American patients with decompensated cirrhosis for a mean duration of 16 months showed that 32 patients (21%) died of liver failure and 78% of the deaths occurred within the first 6 months of therapy, with an estimated actuarial 3-year survival of 88% in patients who survived beyond 6 months. Elevated baseline serum bilirubin and creatinine levels and detectable baseline serum HBV DNA (by the bDNA assay with a lower detection limit of 0.7 MEq/ml) were found to be independent predictors of 6-month mortality during LAM therapy. Early virological response with undetectable serum HBV DNA at 8 weeks of therapy did not correlate with survival [44]. These results indicate that the severity of liver disease at the time of initiating antiviral therapy is a more relevant determinant of early mortality than early virological response, and should be used to guide patient prioritization for liver transplantation. These results again suggest that antiviral therapy must be initiated as early as possible and before the decompensation becomes too severe to be rescued.

It was not clear whether some of the patients in the aforementioned studies evaluating the benefit of LAM therapy in decompensated cirrhosis actually had developed hepatic decompensation due to a hepatitis flare. Nonetheless, several studies on the efficacy of LAM in patients with hepatic decompensation during acute hepatitis flare of CHB have included small number of patients with cirrhosis. All showed similar therapeutic outcomes, including mortality rate, as compared with those without underlying cirrhosis [45–48]. One study showed that initiation of LAM therapy even before the onset of HE did not substantially improve the short-term mortality in comparison with untreated historical controls if the baseline serum bilirubin had already increased over 6 mg/dl with a prothrombin <40% [47], suggesting that suppression of HBV replication at this stage of severe hepatic necroinflammation may be too late to abort the heightened ongoing immune-mediated liver injury. A study in patients with acute exacerbation and decompensation from Taiwan, including 19 patients with cirrhosis, showed that initiation of LAM therapy in patients with a bilirubin level below 20 mg/dl was significantly associated with a lower mortality rate (0% *vs.* 20% in untreated historical controls) but not in patients with a serum bilirubin level increased over 20 mg/dl (67% *vs.* 82% in untreated historical controls) [46]. These results also suggest that oral antiviral therapy should be initiated as early as possible, in the setting of HBV-related acute exacerbation with ensuing or overt hepatic decompensation, and the lower the bilirubin and creatinine the better the prognosis in cirrhotic patients.

Whether LAM therapy decreases the risk of HCC in patients with decompensated cirrhosis remains controversial. In a large randomized placebo-controlled study, LAM therapy for a median duration of 32.4 months was shown to reduce the incidence of HCC and decompensation in patients with advanced fibrosis or compensated cirrhosis (hazard ratio 0.49, $p = 0.047$). However, no protective effect was found in patients whose CTP increased over 7 at the start of drug therapy [35]. Two recent studies showed that virological suppression with LAM did not significantly reduce the incidence of HCC in Child class B and C patients [49,50]. One possible explanation is that cirrhosis is the most important risk factor for HCC as chromosomal aberrations have occurred in cirrhotic nodules [51], and some of the genetic events occurring in HCC may have been present before the initiation of antiviral therapy. Of note, the case number of the patients with decompensated cirrhosis included was small (N = 56) in one study [50] and the median follow-up durations were short (3.0 and 2.7 years, respectively). It remains to be clarified whether Nuc therapy for a longer duration effectively reduces the incidence of HCC in patients with decompensated cirrhosis.

LAM was well-tolerated without significant side effects in all studies. With the approval of high genetic barrier Nucs, ETV and TDF, LAM should not be considered as the first-line therapy in patients with decompensated cirrhosis because of its high rate of resistance over long-term use [29–31]. Nevertheless, lessons learned from LAM therapy in this patient population may be applied in the therapy with other Nucs.

Adefovir dipivoxil

ADV is an acyclic nucleotide analogue of adenosine monophosphate and is active against both wild type and LAM-resistant mutants of HBV. ADV was used at 10 mg daily as a rescue therapy in a study involving 128 wait-listed patients with decompensated cirrhosis who failed LAM therapy and 196 patients with recurrent hepatitis B after liver transplantation. After 48 weeks of treatment, 81% and 76% of the wait-listed and 34% and 49% of the post-transplant patients achieved undetectable HBV DNA (<400 copies/ml) and normal ALT, respectively. The CTP score improved in over 90% of patients in both cohorts. One-year survival was 84% for the wait-listed and 93% for the post-transplant patients [52]. In a long-term follow-up study of the 226 wait-listed patients and 241 post-transplant patients with recurrent hepatitis B due to LAM-resistant HBV, ADV was used for a median duration of 39 and 99 weeks, respectively. Fifty-nine percent and 65% of the wait-listed and 40% and 65% of the post-transplant patients achieved undetectable HBV DNA (<1000 copies/ml) after 48 and 96 weeks of therapy, respectively. After 48 weeks of treatment, liver function improved in 50%-80% of both patient groups. Kaplan–Meier estimates of survival for the wait-listed and post-transplant patients were 86% and 91% at 48 weeks, and 78% and 88% at 96 weeks, respectively. ADV was discontinued due to renal adverse events in 4% of the patients [53].

The efficacy and safety of ADV as a first-line therapy in patients with decompensated cirrhosis have also been demonstrated (see ETV section). Although ADV has a better resistance profile than LAM, its relatively slow HBV DNA suppression and potential risk of drug resistance or renal toxicity remain a concern for its routine use as a first-line therapy in this patient population.

Entecavir

ETV is a deoxyguanosine analogue that belongs to the cyclopentane group. It has a very potent activity against wild type HBV but a weaker activity against LAM-resistant HBV. There are several case series studies using ETV therapy in decompensated patients. A Korean study prospectively compared the efficacy of ETV 0.5 mg daily in 70 patients with decompensated cirrhosis and 144 patients with compensated CHB. They found no significant differences between groups in mean HBV DNA changes, the proportion of patients with undetectable HBV DNA or ALT normalization, rates of HBeAg seroconversion or HBeAg loss after 6 or 12 months of treatment. Of the 55 decompensated patients treated for >12 months, the CTP score and the MELD score improved significantly after 12 months of treatment with 49% showing a decrease of CTP score $\geqslant$2 points and 66% achieving CTP class A status. The 2-year cumulative rates of HCC and death or liver transplantation were 6.9% and 17%, respectively [54]. A study from Hong Kong evaluated the efficacy of ETV in 36 patients with severe acute exacerbation of CHB (five with cirrhosis), in comparison with a historical control group of 117 patients (25 with cirrhosis) treated with LAM. However, patients in the ETV group were significantly older, had lower ALT level, and female dominant. The ETV group had higher mortality in cirrhotic patients (2 of 5 or 40% *vs.* 1 of 25 or 4%, $p = 0.064$) by week 48. However, further analyses showed that the presence of cirrhosis was not associated with mortality [48].

A randomized, open-label, multicenter trial was conducted to assess the safety and efficacy of ETV 1.0 mg as compared to ADV 10 mg daily for 96 weeks in 191 patients with CTP score $\geqslant$7 [55]. As a primary efficacy end point, ETV showed a greater mean reduction in serum HBV DNA from baseline than ADV (−4.48 *vs.* −3.40 $\log_{10}$ copies/ml, p <0.0001) at 24 weeks of treatment. This difference persisted at all time points through week 48. A significantly greater proportion of ETV-treated patients showed HBV DNA <300 copies/ml at 24 (49% *vs.* 16%) and 48 weeks (57% *vs.* 20%), and ALT normalization at 24 (59% *vs.* 39%) and 48 weeks (63% *vs.* 46%) than ADV-treated patients. HBeAg seroconversion rates were similar between groups (6% *vs.* 10%). Among ETV- and ADV-treated patients, a reduction of $\geqslant$2 points in the CTP score occurred in 35% and 27% of patients and mean reductions from baseline in MELD scores were 2.6 and 1.7 at week 48. Cumulative HCC and death rates at week 48 were 12% and 23% for ETV, respectively, and 20% and 33% for ADV, respectively. The 30-day mortality was 2% for ETV and 4% for ADV. Adverse event rates were comparable between groups. Rates of serum creatinine increase $\geqslant$0.5 mg/dl from baseline were 17% for ETV and 24% for ADV. No patients showed resistance in either group at week 48. Although ETV showed superior virological and biochemical improvements over ADV, it did not translate into parallel improvements in hepatic function, HCC occurrence or mortality, at least at 48 weeks of therapy. A follow-up of this cohort is warranted to show whether more potent HBV DNA suppression early on treatment leads to a better long-term outcome.

A study from Germany reported that five of 16 patients with HBV-related cirrhosis developed lactic acidosis between 4 and 240 days after starting ETV treatment [56]. All five patients who developed lactic acidosis had a baseline MELD score $\geqslant$22, thus the MELD score was suggested to be a predictor of the risk of lactic acidosis in patients receiving ETV treatment. However, lactic acidosis was reported in only one subject with a baseline MELD score of 21 on day 1293 of treatment among the 99 ETV treated patients in the trial comparing ETV with ADV in patients with decompensated cirrhosis, and the event resolved with continued ETV treatment [55]. Lactic acidosis was not reported in any of the 70 patients in the Korean study [54] or five patients in the Hong Kong study [48]. Since severe decompensated liver disease *per se* is at risk of lactic acidosis, monitoring this possible lethal complication during Nuc therapy in patients with a high MELD score is needed.

Tenofovir disoproxil fumarate

TDF is an acyclic nucleotide analogue and is structurally similar to ADV. It is active against both wild type and LAM-resistant mutants of HBV and is superior to ADV in HBeAg-negative and HBeAg-positive treatment-naïve CHB patients. It also demonstrated potent antiviral activity in patients with suboptimal response to ADV, mostly with prior LAM exposure. A subgroup analysis of the cirrhotic patients in the HBeAg-negative and

HBeAg-positive registration trials showed similar efficacy and safety to non-cirrhotic patients at 96 weeks of treatment [57].

A randomized, double-blind, multicenter trial assessed the safety of TDF 300 mg/day (N = 45) or a fixed-dose combination of FTC/TDF 200 mg/300 mg per day (N = 45) as compared with ETV 0.5 or 1.0 mg/day (N = 22) for 168 weeks in CHB patients with current or past history of decompensation. Their baseline CTP scores were 7–12 with a median of 7 and a median baseline MELD score of 10 (5–13) [58]. At week 48, tolerability failure rates were 6.7%, 4.4% and 9.1%, respectively. Rates of confirmed serum creatinine increase $\geqslant$0.5 mg/dl from baseline or confirmed serum phosphorus <2 mg/dl were 8.9%, 6.7%, and 4.5%, respectively. The proportions of patients with HBV DNA <400 copies/ml were 70.5%, 87.8%, and 72.7%, respectively. The proportions of patients with ALT normalization were 57%, 76%, and 55%, respectively. HBeAg seroconversion rates were 21%, 13%, and 0%, respectively. A reduction of $\geqslant$2 points in the CTP score occurred in 25.9%, 48%, and 41.7% of patients, respectively, and the median reductions from baseline in the MELD score were 2.0, resulting in a median MELD score of 8 at week 48 in all three groups. There were two deaths in each group, considered to be due to disease progression. No patients developed resistance to any study drug. Thus, all treatments were well tolerated with virological, biochemical, and clinical improvements in this patient population. Combining two TDF-containing arms, Grade 3 or 4 adverse effect was less common (20% *vs.* 53%) and none of the patients with a baseline CTP score $\leqslant$9 died, as compared with those having CTP score >9 (unpublished data). These again suggest that treatment should be started early and before CTP score rises over 9. Although not powered to compare the efficacy, TDF/FTC combination as Truvada seems to have the best therapeutic outcomes. It would be interesting to compare the long-term efficacy and resistance profiles across arms to evaluate the role of combination therapy in this patient population.

A small randomized, double-blind, placebo-controlled study from India evaluated the efficacy of TDF at 300 mg/day in patients with acute-on-chronic liver failure due to spontaneous reactivation of HBV, including some patients with cirrhosis [Ishak fibrosis score 3 (2–6)] but the number of cirrhotic patients was not reported [59]. At admission, patients in the TDF group (N = 14) and the placebo group (N = 13) were severely ill (bilirubin: 24.5 *vs.* 18.2 mg/dl, CTP score: 11 *vs.* 11, and MELD score: 27 *vs.* 25). As expected, the cumulative survival rate at 3 months was significantly better in the TDF group (57% *vs.* 15%). Fifteen of the 17 deaths occurred due to progressive liver failure. The TDF-treated group showed a significant improvement from baseline in the CTP and MELD scores and significant decline in HBV DNA levels. More than 2-log reduction in HBV DNA levels at 2 weeks of treatment was the only independent predictor of survival. Hence, rapid suppression of HBV DNA despite at a time when the heightened immune response is ongoing can stabilize or halt disease progression, and thereby improves prognosis. Although this study clearly demonstrated the expected therapeutic benefit of TDF in patients with acute-on-chronic liver failure, the design of a placebo arm in such critically ill patients recruited in 2007–2009 has provoked great concern.

Telbivudine

LdT is an L-nucleoside analogue and has potent antiviral activity against HBV. A randomized, double-blind, multicenter trial compared the safety and efficacy of LdT 600 mg (N = 114) with LAM 100 mg (N = 114) daily for 104 weeks in patients with decompensated cirrhosis (CTP score >7) [60]. At week 104, a greater proportion of LdT-treated patients achieved HBV DNA <300 copies/ml (49% *vs.* 40%) and ALT normalization (61% *vs.* 52%) than LAM-treated patients. The changes in CTP and MELD scores were comparable between LdT and LAM treated patients. Cumulative HCC and death rates were 15% and 16% for LdT, and 16% and 22% for LAM, respectively. Severe adverse event rates were comparable between groups. Cumulatively, 27% of LdT recipients and 36% of LAM recipients developed genotypic resistance during a 2-year period. These results showed that LdT was well tolerated with the efficacy of stabilizing liver function comparable to LAM. However, both agents were associated with a significant rate of virological breakthrough, which limits their roles as a first-line therapy in this patient population.

Key Points

- Liver disease may continue to progress and decompensation or HCC may occur, especially in cases with active HBV replication. Decompensation may occur at a rate of 2-5% per year
- The 5-year survival rate is 84% in patients with compensated HBV-related cirrhosis, but only 14-35% in patients with decompensated cirrhosis
- Oral antiviral agents are safe and effective in restoring liver function and improving patient survival, especially if therapy is initiated early enough
- The clinical improvement in some wait-listed patients with antiviral therapy can result in their withdrawal from transplant list
- Considering efficacy and drug resistance profile, entecavir and tenofovir are the first-line drugs for HBV-related decompensated cirrhosis
- In the era of nucleos(t)ide analogue, interferon is contraindicated in this patient population
- The preventive effect of antiviral therapy in HCC development has yet to be convincingly demonstrated

Conclusions and perspective

Active viral replication at presentation of cirrhosis is an important factor contributing to further liver disease progression. Decompensation may occur at a rate of 2–5% per year. Once decompensation occurs, the prognosis is poor. Patients with decompensated cirrhosis should be promptly and adequately treated for the decompensating events with relevant current standard of care. Oral antiviral therapy should be instituted regardless of HBV DNA level as early as possible and liver transplantation should be considered (Fig. 2). Each of the five antiviral agents has shown safety and efficacy in improving hepatic function in this patient population. Of note, these studies included different patient population with different severity in terms of CTP/MELD scores and had different aim/design of the trial, as compared in Table 2.

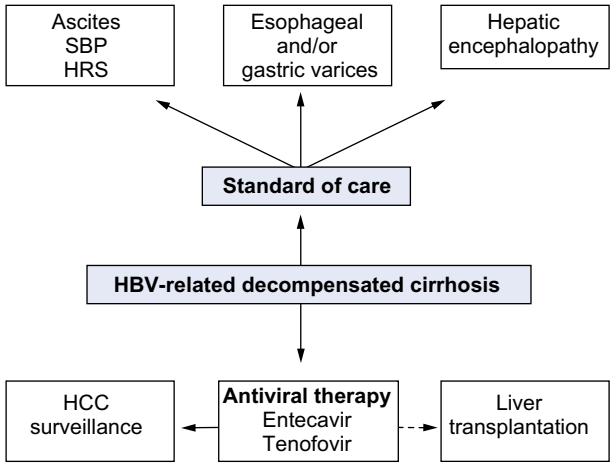

Fig. 2. Management of patients with hepatitis B virus (HBV)-related decompensated liver disease. HCC, hepatocellular carcinoma; HRS, hepatorenal syndrome; SBP, spontaneous bacterial peritonitis.

Taking both efficacy and drug resistance profile into account, ETV and TDF are superior to LAM, LdT, and ADV, and can be considered as the first choice for Nuc-naïve patients with decompensated cirrhosis. However, there are concerns about nephrotoxicity [61,62] and metabolic bone disease observed in human immunodeficiency virus infected patients with TDF treatment [63], although not confirmed in the 48-week report of the trial in HBV monoinfected patients with milder decompensation in terms of baseline MELD and CTP scores [58]. Given that high rate of drug resistance will emerge upon long-term use of ETV 1 mg/day in patients with LAM resistance, TDF is probably a better choice than ETV for LAM or LdT experienced patients.

The preventive effect of antiviral therapy in HCC development has yet to be convincingly demonstrated. The continued follow-up of these ongoing studies will provide more definite recommendations. Finally, decompensated HBV patients receiving oral Nuc(s) must undergo frequent clinical and laboratory assessment to insure medication compliance and surveillance for virological and clinical response as well as drug side effects, drug resistance, and HCC [64].

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Table 2. Oral antiviral therapy in HBV-related decompensated cirrhosis.

Study, [Ref.]	Fontana *et al.*, [44]	Schiff *et al.*, [53]	Shim[a] *et al.*, [54]	Liaw *et al.*, [55]	Liaw *et al.*, [58]	Chan *et al.*, [60]
Drug(s) used	LAM	ADV	ETV (0.5 mg)	ETV/ADV	TDF/TDF + FTC/ ETV[d]	LdT/LAM
Number of patients	154	226	70	100/91	45/45/22	114/114
Baseline data						
LAM resistance, (%)	0	100	0	36/33	18/22/14	0/0
HBeAg-positive, (%)	64	43	49	54/55	31/40/32	37/32
CTP score (class B, C, %)	9 (5-14)[b]	(38, 22)	8.4[c]	8.8/8.4[c] (63, 30)/(67, 22)	7/7/7[b]	8.1/8.5[c]
MELD score	n.r.	n.r.	11.5[c]	17.1/15.3[c]	11/13/10.5[b]	14.7/15.5[c]
HBV DNA level (log_{10} copies/ml)	7.6[b]	7.4[b]	7.2[c]	7.5/8.2[c]	5.7/6.3/5.9[b]	7.6/7.6[c]
1-year efficacy and safety data						
HBV DNA undetectable[e], (%)	>80	59	89	57/20	71/88/73	65/61
ALT normalization, (%)	n.r.	77	76	63/46	46/64/41	65/68
↓ CTP score ≥2, (%)	n.r.	n.r.	49	35/27	26/48/42	32/39
MELD score ↓	n.r.	-2.0[b]	-2.2[c]	-2.6/-1.7[c]	-2/-2/-2[b]	-1.0/-2.0[b]
1-year survival, (%)	84	86	87	77/67	96/96/91	94/88
VB or resistance, (%)	27[f]	2[g]	0[f]	3/7[g]	0/0/0[g]	27/36[g]
Safety issues	LAM resistance related flare	Nephrotoxicity 6%	n.r.	Nephrotoxicity 17%/24%	Nephrotoxicity[h] 9%/7%/5%	Myopathy 1%/0

ADV, adefovir; ALT, alanine aminotransferase; CTP, Child–Turcotte–Pugh; ETV, entecavir; FTC, emtricitabine; HBV, hepatitis B virus; LAM, lamivudine; LdT, telbivudine; MELD, model for end stage liver disease; nephrotoxicity: ↑ creatinine of ⩾0.5 mg/dl from baseline; n.r., not reported; TDF, tenofovir disoproxil fumarate; VB, virological breakthrough.

[a]Fifty five patients who survived 1 year were analyzed for efficacy data.
[b]Median (range).
[c]Mean.
[d]ETV 0.5 mg for <6-month LAM exposure and no history of LAM resistance mutations, 1.0 mg for ⩾6-month LAM exposure and/or a history of LAM resistance mutations.
[e]Lower limit of detection (copies/ml): 7 × 105 [44], 1000 [53], 400 [58], 300 [55,60], 50 [54].
[f]Virological breakthrough.
[g]Resistance.
[h]Nephrotoxicity or serum phosphorus (P) <2 mg/dl.

Conflict of interest

The authors have no financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work. Y.F. Liaw has involved in clinical trials or served as a global advisory board member of Roche, BMS, Novartis and Gilead Sciences.

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