Optimal duration of therapy in HBV-related cirrhosis

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It is estimated that one-third of the world’s population has been exposed to hepatitis B virus and that 300–400 million people have chronic hepatitis B. In areas where hepatitis B infection is endemic, this chronic viral infection is a major cause of premature morbidity and mortality related to hepatocellular carcinoma (HCC) and complications of end-stage liver disease. Recent data from population-based studies suggest that the level of viral replication in chronic hepatitis B is an independent predictor of the future complications of the disease; patients with hepatitis B viral DNA titres $>10^4$ copies/mL (especially those with titres $>10^5$ copies) have a significantly greater risk of developing HCC and cirrhosis. There is also recent evidence that treatment with antiviral therapy in patients with chronic hepatitis B who have advanced hepatic fibrosis is associated with a reduction in the risk of decompensation of liver disease and HCC. Several new antiviral medications have been recently approved for the treatment of chronic hepatitis B. Several recent position statements and practice guidelines have recommended treatment of patients with chronic hepatitis B with oral antiviral medications. However, there remains some disagreement as to the threshold of viral load before treatment should be initiated and the optimal duration of therapy in patients with cirrhosis due to hepatitis B. This article describes the current recommendations regarding therapy in this group of patients and suggests some criteria for treatment of patients with chronic hepatitis B-related cirrhosis or advanced hepatic fibrosis.

Keywords: hepatitis B virus, treatment, chronic HBV

Clinical background

Chronic infection with hepatitis B virus (HBV) is a major cause of liver disease-related morbidity worldwide. Two billion people have been exposed to HBV and 350 million are estimated to have chronic HBV. In the USA, approximately 1.25 million individuals are chronically infected with HBV and 5000 deaths per year are attributed to chronic HBV.

Natural history of chronic HBV

Age and immune competence play an important role in determining the course of HBV infection. The overwhelming majority of patients who acquire HBV through vertical transmission and childhood infection develop chronic HBV. It is estimated that $\sim 13\%$ to $20\%$ of chronic HBV infection in a study in China is secondary to vertical transmission. Among adults who acquire HBV, $<5\%$ become chronically infected. Immune competent adults are more likely to develop acute hepatitis and hepatitis B surface antigen (HBsAg) clearance with subsequent disease resolution than immunocompromised persons.

HBV infection may be categorized into four phases on the basis of the degree of immunological activation and the virus replicative state: immunotolerant, immuno-active, non-replicative and reactivation. Patients in the immunotolerant phase are generally asymptomatic and have high serum HBV DNA levels and hepatitis B e antigen (HBeAg) positivity with normal or minimal elevation of serum liver enzymes. The immunotolerant phase may be followed by an immuno-active phase characterized by an immune response to the high viral load with elevated serum liver enzymes and followed by decreased HBV DNA levels and HBeAg seroconversion to hepatitis B envelope antibody (HBeAb) positivity. Once HBeAg seroconversion takes place, there may be transition to the non-replicative phase, characterized by normal serum liver enzymes and low HBV DNA levels and reduced hepatic necroinflammation. A fourth phase may occur, with reactivation of disease characterized by the elevation of liver enzymes and HBV DNA levels; this may develop spontaneously or may follow a period of immunosuppression. Over the natural history of chronic HBV, patients may develop mutations in the pre-core or core promoter regions of the HBV genome, which may be associated with increased necroinflammation of the liver and persistent HBV DNA replication, although the HBeAg is negative and HBeAb is

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frequently positive. HBeAg-negative chronic hepatitis B appears to have higher rates of progression to cirrhosis (annual rate of 8% to 10%), compared with HBeAg-positive chronic hepatitis B (annual rate of 2% to 5%).

Ongoing HBV replication increases both the risk of developing cirrhosis and hepatocellular carcinoma (HCC) in chronic HBV patients. Other risk factors for the development of cirrhosis in chronic HBV include older age, alcohol abuse, recurrent flares of HBV and co-infection with HIV, hepatitis delta virus (HDV) and hepatitis C virus (HCV). Unlike HCC in the setting of hepatitis C or alcohol, HCC may develop in patients with chronic HBV even in the absence of cirrhosis, although the risk is higher among cirrhotic patients. The presence of HBeAg and HBsAg in the serum is proven to be associated with increased incidence of HCC in chronic HBV.

Current treatment guidelines recommend endpoints that include suppression of HBV DNA replication to undetectable levels (using a PCR-based assay), normalization of serum aminotransferase levels and HBeAg seroconversion (loss of HBeAg and presence of HBeAb). There are several therapeutic agents including interferon-α (IFN-α) and four oral nucleos(t)ide analogues currently approved for the treatment of chronic HBV; several other agents are in late-phase clinical trials.

Treatment of chronic hepatitis B

IFN-α, a cytokine that acts as an antiviral and is also an immunomodulatory agent, was the first treatment used for chronic HBV. Therapy with IFN-α was shown to reduce the incidence of HCC (31% versus 17%, \( P = 0.0124 \)) and liver-related deaths (43% versus 2%, \( P = 0.018 \)) in a 10 year follow-up study. A small proportion of chronic HBV patients who have a virological response with IFN-α may go on to lose HBsAg. Common side effects with IFN therapy include significant neuropsychiatric complications and flu-like symptoms. Rare side effects include myelosuppression and exacerbation of autoimmune disease. IFN is contraindicated in patients with decompensated cirrhosis (Child class B and C) because of risk of worsening liver function.

Lamivudine, an oral cytosine analogue, has been shown to be effective in promoting histological response (i.e. improvement of ≥2 points in the histological activity index) (52% in 1 year), seroconversion from HBeAg to HBeAb (17% in 1 year) and normalization of serum alanine aminotransferase (ALT) level. However, resistance to lamivudine may develop in up to 80% of patients with 4 years of therapy, which has been associated with worsening liver disease and reversal of histology to pretreatment severity. Therefore, the risk of resistance limits significantly the use of lamivudine in patients with cirrhosis and in patients with HBeAg-negative disease in whom long treatment duration may be needed.

Adefovir, an oral nucleotide analogue, has activity against lamivudine-resistant HBV and a lower incidence of resistance than lamivudine. HBeAg-positive patients treated with 10 mg/day had histological improvement after 48 weeks of treatment (53% versus 25%, respectively; \( P < 0.001 \)), reduction in serum HBV DNA levels (median of 3.52 versus 0.55 log copies/mL; \( P < 0.001 \)), normalization of ALT levels (48% versus 16%; \( P < 0.001 \)) and improved HBeAg seroconversion (12% versus 6%; \( P = 0.01 \)) when compared with controls receiving placebo.

The most notable adverse effect of adefovir is nephrotoxicity that may complicate use in patients with advanced liver disease who have renal insufficiency.

Entecavir, an oral nucleotide analogue, is active against wild-type and mutant HBV. Lai et al. conducted a study wherein entecavir was compared with lamivudine in both HBeAg-positive and HBeAg-negative patients over 52 weeks. Entecavir was superior to lamivudine in suppression of HBV DNA level in both HBeAg-positive patients (67% versus 36%, \( P < 0.001 \)) and HBeAg-negative patients (90% versus 72%, \( P < 0.001 \)). Among patients with HBeAg-negative chronic HBV, entecavir was associated with suppression of HBV DNA in 90% of patients after 1 year of therapy. Entecavir was also associated with slightly increased likelihood of HBeAg seroconversion when compared with lamivudine in HBeAg-positive chronic HBV, but the difference was not statistically significant. Entecavir has not yet been evaluated in patients with decompensated cirrhosis in controlled trials.

PEGylated IFN (PEG-IFN)-α-2a is now also approved for the treatment of HBeAg-positive and HBeAg-negative chronic HBV. The combination of an immunomodulatory agent such as PEG-IFN with a nucleoside analogue appears to be an attractive idea for the treatment of HBV. However, results of studies investigating the benefits of combination therapy have been mixed. Janssen et al. found no benefit in combination therapy (PEG-IFN-α-2b and lamivudine) versus PEG-IFN-α-2b monotherapy in HBeAg-positive patients. HBeAg loss rates were 36% at the end of follow-up in both arms. Marcellin et al. performed a trial of PEG-IFN-α-2a monotherapy versus lamivudine monotherapy and the two in combination in HBeAg-negative chronic HBV. Rates of HBV DNA suppression <<400 copies/mL at week 72 were not different between the PEG-IFN-α-2a monotherapy and combination therapy groups (19% and 20%, respectively), but were superior to lamivudine monotherapy (7%, \( P < 0.001 \)). In contrast, Chan et al. found added benefit to combination therapy in HBeAg-positive chronic HBV. During a 3 year follow-up period, there was a higher sustained virological response (defined as loss of HBeAg and HBV DNA <100 000 copies/mL) in those who received both PEG-IFN-α-2b and lamivudine when compared with lamivudine monotherapy (29% versus 9%, \( P = 0.015 \)).

For response to treatment with currently FDA-approved agents for the treatment of chronic hepatitis B (among patients with HBeAg-positive disease), see Figure 1.

Among three major guidelines and published treatment algorithms, there are differences in the treatment recommendations for patients with cirrhosis. These include the threshold level of HBV DNA in the serum at which treatment should be initiated and the optimal duration of therapy.

The specific recommendations within these guidelines for treatment of patients with HBV-related cirrhosis are discussed in the following section.

A US treatment algorithm addressing the role of treatment in various patient groups with chronic HBV was developed by Keeffe et al. in 2004. This algorithm defined a viral load threshold of >10^5 copies/mL for the treatment of HBeAg-positive chronic HBV and >10^6 copies/mL for the treatment of HBeAg-negative chronic HBV. The treatment recommendations for patients with compensated cirrhosis were to initiate treatment at an HBV DNA titre >10^5 copies/mL, regardless of HBeAg status. However, for patients with decompensated cirrhosis,
Keeffe et al. recommended initiation of therapy if any HBV DNA was detectable using a PCR-based assay. The authors suggested that patients with cirrhosis should be treated indefinitely, regardless of HBeAg status and whether traditional endpoints such as HBeAg seroconversion and undetectable HBV DNA were achieved. Keeffe et al. have recently updated their treatment algorithm; the threshold level of HBV DNA for the initiation of therapy in patients with compensated cirrhosis remains 2000 IU/mL (IU = 5.6 copies/mL). In those with decompensated cirrhosis, treatment is recommended at any level of viral replication. The authors recommend indefinite treatment for patients with both compensated and decompensated cirrhosis. Lamivudine is no longer recommended as first-line option for HBeAg-negative patients. First-line options for patients with cirrhosis are entecavir and adefovir, whereas IFN is contraindicated.

Current treatment guidelines

The American Association for the Study of Liver Diseases (AASLD) practice guideline originally published in 2001 by Lok and McMahon recommended initiation of therapy in all chronic HBV patients when HBV DNA level approaches $>10^5$ copies/mL, although they noted that treatment at lower levels of viraemia may be considered for those with decompensated cirrhosis. This treatment guideline did not specify optimum treatment duration for patients with cirrhosis. The only available treatment options at that time were IFN or lamivudine for patients with compensated cirrhosis and lamivudine for those with decompensated cirrhosis. The AASLD practice guidelines have been recently updated for 2007. The level of viraemia to initiate therapy in patients with compensated cirrhosis is HBV DNA $\geq 2000$ IU/mL, although treatment at lower levels was endorsed among patients with lower levels of viraemia in the presence of elevated liver enzymes or other signs of active liver disease. These guidelines also recommend that PEG-IFN or IFN be avoided in patients with cirrhosis and that preferred therapies include entecavir or adefovir, with consideration of combination therapy with lamivudine and adefovir or entecavir in patients with decompensated cirrhosis. Both the US treatment algorithm and the AASLD practice guidelines emphasize the importance of early referral to a transplant centre in patients with decompensated cirrhosis.

The European Association for the Study of the Liver (EASL) international consensus conference statement on hepatitis B published in 2003 similarly recommended that patients with compensated cirrhosis should be managed like non-cirrhotic patients. The first-line treatment recommended in this statement was a 4–6 month course of IFN-$\alpha$, followed by lamivudine or adefovir for at least 1 year and for 6 months after virological response. Virological response was defined as HBV DNA levels below $10^5$ copies/mL and disappearance of HBeAg in HBeAg-positive patients. For HBeAg-negative patients, a course of IFN-$\alpha$ was recommended for 12–24 months. There was no optimal treatment duration recommendation made for HBeAg-negative patients treated with lamivudine/adefovir.

The Asian-Pacific Association for the Study of the Liver (APASL) consensus statement was published in 2003 and updated in 2005. The APASL recommendations regarding treatment of patients with compensated cirrhosis were the same as for those without cirrhosis. IFN-$\alpha$ was recommended as the first-line treatment for a duration of 4–6 months for HBeAg-positive chronic HBV and for 12 months for HBeAg-negative chronic HBV, regardless of virological or serological response. Two oral antiviral agents, lamivudine and adefovir, were also included as initial treatment options for HBeAg-positive and HBeAg-negative patients. The APASL treatment recommendations also outlined endpoints of therapy; the authors suggested that lamivudine/adefovir may be discontinued in HBeAg-positive patients after HBeAg seroconversion if accompanied by undetectable HBV DNA levels on two occasions at least 6 months apart; in HBeAg-negative patients, endpoints of treatment were defined.
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as undetectable HBV DNA in serum and normal ALT on three occasions over a 6 month period.

In summary, there are divergent opinions in the literature from consensus statements of learned societies and experts on the optimal duration of therapy for HBV-related cirrhosis and compensated liver function. Some have suggested lower threshold levels of HBV DNA to initiate therapy and indefinite treatment, whereas others have not differentiated the management of cirrhotic patients differently from those without cirrhosis (AASLD, EASL and APASL). Furthermore, some position papers have excluded IFN treatment for all patients with cirrhosis (AASLD and Keeffe), whereas others have suggested that IFN should be a first-line therapy (EASL and APASL). Nevertheless, there appears to be a growing trend towards lower thresholds of viraemia to initiate therapy in patients with cirrhosis and long-term indefinite therapy with a goal of suppression of HBV DNA replication.

To date, there is only one controlled trial published to support long-term antiviral therapy (lamivudine) in chronic HBV patients with advanced liver disease. Liaw et al.28 conducted a large randomized study among patients with chronic HBV and advanced hepatic fibrosis of lamivudine versus placebo to examine the effect of treatment on liver disease decompensation and incidence of HCC. The study was stopped prematurely at 32 months because of a reduced rate of decompensation of liver disease and HCC in the lamivudine-treated patients. However, the study did not publish data of HBeAg seroconversion rates for the treatment arm, which may have shown that the clinical benefits are primarily observed among patients with HBeAg seroconversion.

Two recent large prospective studies of >3000 subjects with chronic HBV from Taiwan showed that serum HBV DNA level >10⁴ at baseline was an independent predictor of development of cirrhosis and HCC over 11 years of follow-up after adjustment for HBeAg status, age, sex, serum ALT level, tobacco and alcohol consumption.29,30

In considering the optimal duration of treatment in chronic HBV, the clinician needs to balance the potential benefits of reduction in risk of HCC and liver disease decompensation with the costs of long-term therapy, the possible emergence of drug-resistant mutants with continued exposure to the nucleoside and nucleotide analogues and the possibility that there may be a flare of liver disease if treatment is discontinued.

In our opinion, treatment with IFN or PEG-IFN should be avoided in patients with cirrhosis even if the liver function is normal and there is no evidence of portal hypertension. Long-term, indefinite therapy with oral antiviral medication is appropriate as long as there is evidence of circulating viraemia, even if the titres are low (≥2000 IU/mL). Treatment should focus on regimens with high potency and low risk of resistance, such as entecavir or adefovir. In patients with cirrhosis, active viral replication and a history of lamivudine resistance, combination therapy with entecavir and tenofovir or entecavir and adefovir is reasonable.

The care of patients with cirrhosis related to chronic hepatitis B should also include attention to routine preventive health measures that apply to all patients with cirrhosis. Screening for oesophageal varices using endoscopy is appropriate every year to every other year. Non-selective beta-blockers should be used to reduce the risk of variceal bleeding in patients with moderate or large varices. Prophylactic antibiotics should be used to prevent spontaneous bacterial peritonitis (SBP) among patients with ascites or a history of SBP. Vaccination against hepatitis A is appropriate among patients without evidence of previous exposure. Screening for HCC with serum alpha fetoprotein and ultrasonography or CT scanning should be conducted on a regular basis.

In summary, there is no conclusive evidence that indefinite therapy is warranted after HBeAg seroconversion among patients with wild-type chronic hepatitis B and compensated cirrhosis; long-term, indefinite therapy has been advocated for patients with pre-core variant chronic hepatitis B (HBeAg-negative disease). It is reasonable to conclude that for patients with decompensated cirrhosis, indefinite therapy is important as suppressive therapy may reduce the risk of graft re-infection following liver transplantation and the risk of a life-threatening relapse associated with recurrent viraemia if treatment discontinued.

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