Management of End-Stage Liver Disease in Chronic Hepatitis B

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KEYWORDS

• Hepatitis B • Liver transplantation • End-stage liver disease
• Cirrhosis • Antiviral therapy

Chronic hepatitis B virus (HBV) is the most common cause of chronic viral hepatitis and end-stage liver disease worldwide, with more than 350 million individuals chronically infected.[1,2] For details on the disease burden of HBV infection in the United States, see the article by Kim elsewhere in this issue. Chronic HBV may result in cirrhosis, liver failure, or hepatocellular carcinoma (HCC).[3] Hepatic decompensation usually presents 3 to 5 years from the recognition of cirrhosis[4] and is accompanied by a significant decrease in survival to less than 35% at 5 years.[5,6] For further details on the natural history of chronic HBV infection, see the article by McMahon elsewhere in this issue.

ANTIVIRAL THERAPY IN ADVANCED CHRONIC HEPATITIS B

Therapeutic goals in the patient with chronic HBV with cirrhosis include complete viral suppression, sustained HBeAg seroconversion (where applicable), the prevention or even reversal of hepatic decompensation, reduction of HCC risk, and prevention of viral recurrence after transplantation. Large-scale studies with adequate follow-up periods have confirmed a relationship between viral replication (reflected in serum HBV DNA levels) and development of cirrhosis[7] and HCC.[8] Further results and implications of the Taiwanese REVEAL study are described in the article by McMahon elsewhere in this issue. Detectable viremia before liver transplantation (OLT) is associated with reduced patient and graft survival because of HBV recurrence in the graft,[9–13] underscoring the importance of achieving viral suppression before OLT.

Antiviral therapy is indicated in all cirrhotic patients with evidence of active HBV viral replication (HBV DNA >2000 IU/mL), regardless of alanine aminotransferase (ALT)

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levels or HBeAg status.[14,15] It is also indicated in all decompensated cirrhotic patients with increased ALT levels if HBV DNA is detectable (regardless of titer).[15] Viral flares are less well tolerated in the patient with end-stage liver disease and may result in clinical deterioration or death,[16,17] hence the importance of achieving viral suppression in such patients and the importance of treatment compliance. Some investigators also advocate antiviral therapy for cirrhotic patients even in the absence of viral replication.[14] Antiviral prophylaxis with nucleos(t)ide analogues is also indicated in the aviremic patient with HBV who requires immunosuppressive or cytotoxic chemotherapy. Prophylaxis should be commenced before immunosuppressive therapy and continued throughout the course of treatment.[15,18]

Once antiviral treatment with nucleos(t)ide analogues is commenced, treatment is usually life-long in cirrhotic patients, as interruption of therapy is associated with a risk of viral reactivation, hepatic decompensation,[19,20] and histologic regression despite benefit while on therapy.[21,22]

Monotherapy and Choice of Agent

Interferon alpha-2a

Interferon alpha-2a, standard and pegylated formulations, has been approved by the US Food and Drug Administration for the treatment of chronic HBV infection. Interferon enhances host response to HBV infection, resulting indirectly in HBV clearance. Interferon directly inhibits hepatic stellate cell activation.[23] In animal models, it has been shown to reduce collagen gene transcription[24] and reverse cirrhosis.[25] Long-term studies confirm that interferon promotes viral clearance and prevents the development of cirrhosis, clinical decompensation,[26–28] and development of HCC.[29] However, its use in advanced liver disease is potentially hazardous as it may precipitate clinical decompensation, increasing the risk of bacterial infection by inducing an imminent viral flare,[30–32] even with low doses. For these reasons, interferon therapy in decompensated HBV cirrhosis is contraindicated.[14,15] In the well-compensated HBV cirrhotic patient, however, there was no difference in the need for dose reduction or discontinuation of interferon therapy compared with noncirrhotic patients.[33] Also, registration trials for pegylated interferon alpha-2a did not result in hepatic decompensation despite advanced fibrosis in some subjects,[34–36] although viral flares with ALT levels increased more than 5 times the upper limit of normal were reported, suggesting that there may be a role for pegylated interferon in well-compensated cirrhosis.[14]

Nucleos(t)ide analogues

Nucleoside (lamivudine, entecavir, telbivudine) and nucleotide (adefovir dipivoxil, tenofovir disoproxil fumarate) analogues of the HBV DNA polymerase are approved for chronic HBV therapy in the United States and elsewhere. Nucleos(t)ide analogues have shown benefits in delaying disease progression, stabilizing or even reversing hepatic decompensation, promoting histologic improvement,[37–39] and salvaging patients with decompensated HBV disease.[40–42] Nucleos(t)ide analogues have the advantage of profound viral suppression and safety, even in decompensated cirrhosis. Since their introduction, the number of candidates listed for OLT for decompensated cirrhosis caused by HBV in the United States has fallen significantly.[11]

Lamivudine was the first licensed oral agent studied in advanced liver disease. Studies have demonstrated effective viral suppression, prevention of disease progression in advanced fibrosis,[43] survival benefit,[41] and improved clinical outcomes reducing the need for OLT.[44–47] However, in view of its resistance profile (70% drug resistance at 5 years),[48] lamivudine monotherapy is no longer the treatment of choice for patients with chronic HBV.[14,15]