



## Treatment of Hepatitis B Virus Cirrhosis

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Untreated Hepatitis B Virus (HBV) cirrhosis runs a progressive course to liver failure and death. However, new antivirals that adequately control HBV replication can interrupt this ominous clinical course, are capable of reverting liver fibrosis and may avoid liver transplantation. Therefore indefinite treatment with the latest generation antivirals (Entecavir, Tenofovir) has become mandatory in all HBV viremic patients with compensated and decompensated cirrhosis

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An analysis of cohorts of patients with compensated cirrhosis caused by the Hepatitis B Virus (HBV) indicates that the disease decompensates at an annual rate of 1.5% to 5%. Following decompensation, the 5-year survival rate has varied from 14% to 35% (1); the 5-year survival rate in untreated patients is higher in patients decompensating from variceal bleeding than in those decompensating from ascites (29 vs. 16%) (2). Given its ominous course, it is of no surprise that international guidelines recommend treating HBV cirrhosis to control HB viremia, prevent the dire complications of the disease, and increase survival. Interferon is an unfit treatment solution. It is contraindicated in decompensated cirrhosis and of limited use in compensated cirrhosis (3, 4). HBV can usually only be controlled for temporarily; the cytokine cannot be given for long because of side effects and bacterial infection; and exacerbation of liver disease can decompensate the disease. Antiviral therapy for HBV cirrhosis entered common practice following the seminal study of Dr. Liaw (5),

who showed that the treatment of compensated HBV cirrhosis with Lamivudine significantly diminishes the risk of decompensation and complications; specifically, after 36 months of therapy, only 9% of the patients in Lamivudine treatment experienced progression of the disease, versus 21% of those in the placebo group, a difference so significant that it prompted early termination of the trial. Unfortunately, Lamivudine treatment is aggravated by a high risk of viral resistance and hepatitis flares; these conditions can cause rapid deterioration of the liver disease and death (6). Adefovir, the next antiviral to be developed, confirmed the efficacy of treatment for HBV cirrhosis, in particular in the transplantation setting. In two studies, patients with lamivudine-refractory-decompensated HBV were given Adefovir for 1 year; at the 1-year mark, these patients had significantly improved the Meld score versus baseline (7, 8). However Adefovir was not perfect, as it had a potential for nephrotoxicity (a particular risk in cirrhotic patients) and suppressed HBV replication only slowly. Furthermore, the patients' experience with Lamivudine suggested that therapy was of no immediate benefit to the cirrhotic patients, some of whom died early despite therapy. A survival advantage became apparent only after 6 months of therapy, indicating that patients with the most severe disease progres-

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sions had not improved regardless of HBV repression. The message is obviously to treat cirrhosis with the efficacious drugs before the disease reaches a point of no return (9). The advent of second-generation antivirals such as Entecavir and Tenofovir has offered better therapeutic prospects. Studies were completed on the efficacy and safety of Entecavir both in patients with compensated and decompensated HBV cirrhosis. In cases of compensated cirrhosis, Entecavir was shown to inhibit HBV replication more rapidly and effectively than either Lamivudine or Adefovir, with no significant toxicity (10, 11). Entecavir is safe and effective in decompensated cases as well. In a cohort of 70 consecutive Korean patients with decompensated HBV cirrhosis (12), treatment led to more than a 2-point decrease of the Child-Pugh score for 50% of patients. Additionally, HBV-DNA became undetectable in almost 90% of patients, HBeAg loss was experienced by 48% of patients, and a 1-year transplant-free survival rate was experienced by 87% of patients. Controlling HBV was warranted in all patients during the 1-year follow-up. In a study in Taiwan (13), the outcome of decompensated HBV cirrhosis was compared between patients treated for 96 weeks with Entecavir and patients treated for 96 weeks with Adefovir. Entecavir was superior, reducing HBV-DNA at all-time points and improving the Meld score at Week 48 of therapy (down 2.6 points from baseline). In 2009 concern was raised that Entecavir might cause lactic acidosis because the drug was reported to induce this metabolic condition in patients with advanced liver disease (14). However, further studies have dispelled this concern; only one case of lactic acidosis was reported among Entecavir recipients in clinical trials (15), and in a small controlled study of critically ill patients, no difference in lactacidemia was observed between patients who received Entecavir and those who went untreated (16). Similarly good performance has been reported for Tenofovir (17). One study compared 45 patients with decompensated cirrhosis who were treated with Tenofovir, 45 patients who were treated with Tenofovir and Emtricitabine, and 22 patients who were treated with Entecavir. At week 48, HBV-DNA was undetectable in 70.5% of the first group, 87.8% of the second group, and 72.7% of the third group. Liver enzymes returned to normal in 57%, 76%, and 55% of patients, respectively and seroconversion to anti-HBe occurred in 21%, 13%, and 0%, respectively. Long-term control of HBV with antivirals has important benefits. Survival distinctly increases in HBV cirrhosis given antivirals compared to untreated patients (2). The impact has been dramatic in the liver transplant setting; the widespread application of antiviral therapy for HBV has contributed to diminish the demand for HBV transplants; a distinct proportion of patients exhibit clinical ameliorations that are significant enough to permit their withdrawal from the transplant list (8). Unexpected yet most encouraging, cumulative data from registrative trials of Entecavir and Tenofovir have shown that long-

term control of HBV results in significant reduction of fibrosis. Of 57 patients responding for 3 years to Entecavir for whom paired liver biopsies were available, 88% exhibited a regression of fibrosis with a decrease in the Ishak fibrosis score of more than 1 point, including 10 patients with advanced fibrosis (18). Of 94 patients responding for 240 weeks to Tenofovir for whom paired biopsies were available, 72% exhibited a regression by at least 2 points in the Ishak fibrosis score (19). In keeping with the histological data, the hepatic venous pressure gradient diminished in all but 1 of 19 patients just after 1 year of Lamivudine therapy (5); thus amelioration of liver fibrosis at morphology appears to be functionally matched by a decrease of portal hypertension. The unfortunate news is that antiviral treatment diminishes but does not eliminate the risk of hepatocellular carcinoma. In a systematic analysis of 3,881 Lamivudine-treated and 534 untreated patients during a median 46-month period, hepatocellular carcinoma was diagnosed in 6.4% of untreated patients but also in 2.8% of treated patients (20). The EASL Clinical Practice Guidelines (1) recommend treating HBV cirrhosis that exhibits any level of HBV-DNA, either compensated or decompensated, with potent antivirals that have very low risk of resistance (i.e. Tenofovir and Entecavir). Lamivudine is not recommended; if used because of local policy, Lamivudine should be used in combination with Tenofovir.

## Authors' Contribution

Completley done by Rizzeto M.

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None declared.

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