Reversibility of Hepatic Fibrosis and Cirrhosis—Another Evidence

Abstract

Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, Washington MK, Germanidis G, Flaherty JF, Schall RA, Bornstein JD, Kittrinos KM, Subramanian GM, McHutchison JG, Heathcote EJ. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet*. 2013;381:468–475.

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Background: Whether long-term suppression of replication of hepatitis B virus (HBV) has any beneficial effect on regression of advanced liver fibrosis associated with chronic HBV infection remains unclear. We aimed to assess the effects on fibrosis and cirrhosis of at least 5 years' treatment with tenofovir disoproxil fumarate (DF) in chronic HBV infection.

Methods: After 48 weeks of randomized double-blind comparison (trials NCT00117676 and NCT00116805) of tenofovir DF with adefovir dipivoxil, participants (positive or negative for HBeAg) were eligible to enter a 7-year study of open-label tenofovir DF treatment, with a pre-specified repeat liver biopsy at week 240. We assessed histological improvement (≥ 2 point reduction in Knodell necroinflammatory score with no worsening of fibrosis) and regression of fibrosis (≥ 1 unit decrease by Ishak scoring system).

Findings: Of 641 patients who received randomized treatment, 585 (91%) entered the open-label phase, and 489 (76%) completed 240 weeks. 348 patients (54%) had biopsy results at both baseline and week 240. 304 (87%) of the 348 had histological improvement, and 176 (51%) had regression of fibrosis at week 240 ($P < 0.0001$). Of the 96 (28%) patients with cirrhosis (Ishak score 5 or 6) at baseline, 71 (74%) no longer had cirrhosis (≥ 1 unit decrease in score), whereas three of 252 patients without cirrhosis at baseline progressed to cirrhosis at year 5 ($P < 0.0001$). Virological breakthrough occurred infrequently and was

not due to resistance to tenofovir DF. The safety profile was favourable: 91 (16%) patients had adverse events but only nine patients had serious events related to the study drug.

Interpretation: In patients with chronic HBV infection, up to 5 years of treatment with tenofovir DF was safe and effective. Long-term suppression of HBV can lead to regression of fibrosis and cirrhosis.

COMMENTS

Enough evidence now exists in the literature that even advanced hepatic fibrosis which was once thought to be irreversible, can be reversed if the underlying cause of liver injury is taken care off. The evidence exists for many liver diseases including patients with chronic hepatitis C virus treated with interferon,¹ patients undergoing biliary drainage for common-bile duct obstruction in chronic pancreatitis,² hepatic schistosomiasis treated with praziquantel,³ and venesection therapy for genetic haemochromatosis.⁴ Similar evidence is available in patients with chronic hepatitis B (CHB) with advanced fibrosis and cirrhosis, but is limited to either the first generation of oral drugs or to small number of patients.^{5–10} One of such studies by Liaw et al using Lamivudine was the initial proof of the concept studies in this area.⁶ They included 651 patients (98% – Asians) in a double-blind, randomized, placebo-controlled trial. The study included patients with bridging fibrosis or cirrhosis and high levels of HBV replication (HBe-positive and/or serum HBV DNA $> 700,000$ c/mL). After a median period of 32.6 months when the study was prematurely terminated, they showed significantly reduced risk of disease progression, onset of clinical decompensation and development of HCC in the Lamivudine group.⁶ Though a landmark study, it was limited to Asian patients with high viral load and did not adequately assess the histological reversal of advanced fibrosis or cirrhosis. Moreover, because of the high drug resistance, Lamivudine is not the drug of choice in patients with cirrhosis liver. Of the high genetic barrier drugs entecavir was evaluated in one of the studies which included sixty-nine patients [50 HBeAg-positive and 19 HBeAg-negative] with high baseline HBV DNA.¹⁰ For inclusion in the study, patients had received at least 3 years of entecavir therapy and the median time of biopsy was at 6 years (range = 3–7 years). Repeat biopsy was done in 57 patients and ≥ 2 -point decrease in the Knodell necroinflammatory score was shown in

96% of patients and ≥ 1 -point improvement in the Ishak fibrosis score was documented in 88% of patients including 10 patients with advanced fibrosis or cirrhosis at baseline.¹⁰ This study was important since it looked at the histological improvement with a very potent drug with minimal risk of drug resistance on long-term use but was limited by the small number of patients with advanced fibrosis or cirrhosis.¹⁰

The recent study by Marcellin et al has taken the same concept forward with another high genetic barrier drug (tenofovir) demonstrating its efficacy in reversibility of advanced fibrosis and cirrhosis in a large number of patients with CHB.¹¹ Of the 585 patients (positive or negative for HBeAg, high HBV DNA) of a 7-year – open-label tenofovir trial, 489 (76%) patients who completed 240 weeks of treatment were included in the study. 348 patients (54%) had a liver biopsy at baseline and week 240. Of these 304 (87%) patients showed histological improvement and 176 (51%) patients showed regression of fibrosis ($P < 0.0001$) with tenofovir treatment. Ninety-six (28%) patients had cirrhosis (Ishak score 5 or 6) at baseline and at the end of treatment, 71 (74%) of these patients no longer had cirrhosis showing ≥ 1 unit decrease in their fibrosis score.¹¹ The strengths of the study by Marcellin et al¹¹ include that it has evaluated a potent drug with high genetic barrier in a large number of patients including sufficiently large number of patients with advanced fibrosis and cirrhosis. Histological assessment at baseline, year 1, and year 5 has not only shown that long-term suppression of HBV can lead to regression of fibrosis and cirrhosis but has also shown that tenofovir DF given for up to 5 years is safe and effective with no drug resistance at 5 years.¹¹ But like previous studies this study was also done in patients with high viral load, hence cannot answer the utility of such intervention in patients with advanced fibrosis and cirrhosis with low viral load.

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