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Liver fibrosis reversion after suppression of hepatitis B virus

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Introduction

Hepatitis B virus (HBV) infection causes a huge burden of disease worldwide. With the advent of ever expanding and highly effective compounds that suppress or even eradicate this virus, great strides have been made.

HBV infection is complicated in many regards, not only by the complexities of the virus and hepatocyte interaction, but also by the host immune response. It typically causes chronic inflammation, the precursor to hepatic fibrogenesis¹. In the liver, ongoing fibrogenesis ultimately leads to cirrhosis. HBV cirrhosis affects millions of patients worldwide and is responsible for an extremely high burden of disease².

Treatment of patients with HBV with nucleos(t)ide analogues is well known to lead to rapid suppression of HBV replication with concomitant reduction in inflammation. Further, this suppression of inflammation provides an intrahepatic milieu such that fibrosis reverses, and further, an improvement in liver function and even survival in patients with complications of cirrhosis. In fact, the data in this area are overwhelmingly positive.

Reversibility of fibrosis and cirrhosis

There is now extensive evidence that liver fibrosis regresses, both in experimental models³ and in human liver disease (for the purposes of this discussion, it is assumed that reversion of fibrosis occurs along a continuum — whether linear or not, and that reversion of fibrosis and reversal of fibrosis may be partial or even complete). These data are highly consistent with the idea that liver wounding, as well as that in essentially all parenchymal organs, is a dynamic one that includes both matrix synthesis and deposition and matrix degradation^{1, 4}.

Further, the data also suggest that fibrosis and even cirrhosis regression is characteristic of virtually all forms of liver disease, and occurs in both experimental models^{3, 5, 6} and in human liver disease^{7–14} (Figure 1). Currently available data suggest that in order for fibrosis

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to regress, the underlying disease must be treated-held in check or cured. This is especially true for liver diseases in which inflammation drives the fibrotic response (see below). Consistent with this concept are data in the HBV field in which there is fairly extensive evidence^{10, 15–18}. Active HBV typically drives inflammation and aggressive fibrogenesis, and elimination of this inflammatory response is associated with a reduction in fibrosis. Further, data are also now emerging in patients with HCV^{19–21}. Further, evidence exists in many other liver diseases as well, including delta hepatitis²², hemochromatosis^{23, 24}, removal of alcohol in alcoholic liver disease²⁵, decompression of biliary obstruction in chronic pancreatitis¹², immunosuppressive treatment of autoimmune liver disease¹⁴, and schistosomiasis²⁶.

Basic mechanisms

The pathogenesis of all forms of fibrosis is linked to a population of effector cells that produce abnormal amounts of extracellular matrix that is deposited in parenchymal tissue and disrupts organ function¹. Further, implicit in this biology is that fibrosis is dynamic, and that there is not only deposition of extracellular matrix, but also that there is also resorption of this matrix. When imbalanced, the result is exaggerated fibrosis, or reversion of fibrosis (Figure 2).

In the liver, the primary effector cell is the hepatic stellate cell (Figure 3), which exhibits a number of key phenotypic characteristics during its activation that in turn drive the fibrogenic response⁴. In most forms of fibrogenesis, inflammation is a core driver of the fibrotic lesion (Figure 4). This is particularly noteworthy in patients with HBV fibrosis and cirrhosis.

There are undoubtedly multiple mechanisms underlying fibrosis regression. A core concept is that during reversal of fibrosis, there appears to be a specific reduction in stellate cell activation (Figure 5). Extensive data indicate that in cell culture models, stellate cells can be manipulated such that they undergo a transition from an activated to a quiescent state^{27, 28}. This phenotypic reversal also occurs *in vivo*, although “deactivated” stellate cells appear to exhibit greater responsiveness to recurring fibrogenic stimulation²⁹. Apoptosis of stellate cells also likely accounts for the decrease in number of activated stellate cells typical of resolution of hepatic fibrosis *in vivo*³⁰. Apoptosis may be inhibited by factors present during injury, or stimulated by other factors as the injury is removed. Additionally, molecules regulating matrix degradation appear closely linked to survival and apoptosis. For example, MMP2 activity correlated with apoptosis, and MMP2 may be stimulated by apoptosis³¹. Inhibition of MMP2 activity by TIMP-1 also blocks apoptosis in response to a number of apoptotic stimuli³².

Additionally, programmed cell death appears to be linked to autophagy, which appears to stimulate stellate cell activation, and may contribute to the fibrogenic cascade^{33–36}. Cellular senescence has also been proposed to play a role in fibrosis resolution^{37–39}, though the evidence for this in stellate cells is modest.

Clinical considerations

The evidence that effective long-term treatment of patients with HBV and advanced liver fibrosis and even cirrhosis improves clinical outcomes is convincing. Several clinical considerations are noteworthy (Box 1). One of the more convincing studies convincingly established this concept¹⁰. In this trial of patients with HBV and advanced fibrosis (Ishak stage 4 or greater) who received lamivudine or placebo, 8% of patients receiving lamivudine and 18% percent of those receiving placebo developed hepatocellular carcinoma, spontaneous bacterial peritonitis, bleeding gastroesophageal varices, or had death related to liver disease ($P=0.001$) (Figure 6)¹⁰. Although fibrosis regression was not documented histologically, other data in the field (see below) suggest that the mechanism for the response was almost certainly fibrosis regression. A final point is that for reversion of fibrosis or cirrhosis to be sustained, suppression of HBV replication (with normalization of alanine aminotransferase (ALT)) is essential. A recurrent theme is that the beneficial effects of treatment are not found when there is breakthrough.

Fibrosis reversion after HBV suppression

Multiple agents with which to treat HBV are currently available. The evidence suggests that so long as viral replication and the concomitant inflammatory response is suppressed, fibrosis will reverse. Thus, it probably does not matter so much which antiviral agent is used, but rather that it is important that the virus be suppressed or eliminated.

An important question to be addressed is exactly how much fibrosis regression should be expected? In one of the largest histological studies of paired pre- and posttreatment liver biopsies⁴⁰ treated with an antiviral agent (in this study, tenofovir), 348 patients with HBV and advanced fibrosis had liver histology assessed at baseline and at 5 years (Figure 7). In this group, viral suppression (HBV DNA <400 copies per mL) was documented in 330 (99%) of the 334 patients for whom viral load data were available. In the 96 patients (28%) with histological cirrhosis (defined as Ishak score ≥ 5) at baseline, 71 (74%) had a reduction in fibrosis at year 5 (and thus did not have histological cirrhosis). The difference between the proportion of patients with cirrhosis regression and without cirrhosis that progressed to cirrhosis (1%) was highly significant ($p<0.0001$). Further, all but one with regression had a reduction of at least 2 units in the Ishak score at year 5, and more than half (58%, 56 patients) had a decrease of 3 units or more. In the 252 (72%) patients that did not have histological cirrhosis (Ishak score ≤ 4) at baseline, 12 (5%) had worse fibrosis at year 5; 135 (54%) had no change, and 105 (42%) had improvement. Nine of 12 patients with worsening had an increase in fibrosis score of 1 unit, and three patients (1%) progressed to cirrhosis.

In terms of the different HBV antiviral agents, they all appear to have substantial effectiveness in terms of their effects on reversion of advanced fibrosis (^{40–47}, Table 1). It should be emphasized that the general trends in terms of regression are remarkable, and that a majority of patients, but not all patients, should be expected to have fibrosis regression. Again, it is important to emphasize that this occurs in the setting of suppression of viral replication. Interestingly, it is unclear why some patients do not exhibit reversion of fibrosis, although it may be speculated that this has to do with host specific fibrogenic factors.

In terms of the duration of treatment, the data suggest long-term therapy is desirable. In the above study (Figure 7, and⁴⁰) of tenofovir, this agent appeared to be safe and effective when given for 5 years, and there is no reason to believe that even longer term treatment would not be safe. Further, given the natural history of HBV cirrhosis, it is expected that the longer the durability of viral suppression, the greater the effect on clinical outcomes.

Measurement of fibrosis

Measurement of fibrosis is important for several reasons. First, it helps to stage liver disease, but also to monitor fibrosis after therapy. There is considerable controversy about how to best measure fibrosis. Liver biopsy and histology, long considered to be the gold standard is invasive, and may be subject to sampling error⁴⁸. Clinical methods (use of physical findings, and routine laboratory tests such as platelets alone) are typically insensitive and not specific. A plethora of blood based test algorithms and serum markers of fibrosis (i.e. TIMP1, MMP2, collagen I, III, IV, hyaluronic acid, and others) have been developed and studied extensively in patients with HCV. Several have also been examined in HBV. The bulk of the data suggest that these tests have a high sensitivity and specificity for detection of far advanced fibrosis and cirrhosis, but are not highly sensitive or specific for less advanced stages of fibrosis⁴⁹. Additionally, several imaging modalities, in particular vibration control transient elastography (also simply transient elastography) and magnetic resonance elastography are attractive to stage fibrosis because they are non-invasive. Like blood tests and serum marker panels, they are best for advanced fibrosis and cirrhosis, and less sensitive and specific for intermediate degrees of fibrosis⁴⁹. It is clear that more research will be required in the area of monitoring of fibrosis regression.

Anti-fibrotic therapy

Since the degree of liver fibrosis is highly desirable because it appears to lead to the complications of chronic liver disease, including impaired synthetic function, liver failure, and perhaps hepatocellular cancer. Fibrosis is also tightly linked to portal hypertension. Although attempts have been made previously to specifically treat the “fibrosis” component of liver disease, these approaches have generally been unsuccessful (see^{1, 4} for review). Thus, fibrosis represents a major unmet need in the field.

As highlighted above, the most effective “anti-fibrotic” therapies are clearly those that treat or remove the underlying stimulus to fibrogenesis. With highly active and effective nucleos(t)ide analogues, this issue is important. Not only would it be expected for an antifibrotic agent to have beneficial effects in this population, but certain mechanistic approaches might be particularly attractive. For example, a compound that affects collagen crosslinking that might break down formed fibrous tissue, such as lysyl oxidase-like-2⁵⁰, is attractive.

Reversion of fibrosis and outcomes with viral suppression

Abundant evidence in the HBV field indicates that treatment of patients with advanced fibrosis and cirrhosis - and with complications of HBV cirrhosis, including with esophageal varices, ascites, hepatic encephalopathy, and coagulopathy - with nucleos(t)ide analogues improves outcomes^{10, 51–57}. The evidence that this is related to fibrosis reversion is

correlative, but is supported by data that indicate that treatment of patients with nucleos(t)ide analogues not only reduces fibrosis, but also has effects on portal hypertension. Notwithstanding, it is important to recognize that even though fibrosis may be improved, the pathologic deposition of extracellular matrix and subsequent alteration in sinusoids and in blood flow may not necessarily be reversed. Since outcomes appear to be most closely tied to portal hypertension, this point is critical.

The natural history of HBV cirrhosis suggests that after the development of complications, prognosis is poor, with a 5-year survival of approximately 25%. In contrast, although the long-term mortality in patients with complications of HBV cirrhosis after treatment with an oral HBV antiviral agent is not entirely clear, the 1 year survival for these patients is typically over 80% and may be over 90%^{51–57}. Essentially all of the currently used oral antiviral agents (lamivudine, adefovir, entecavir, telbivudine, or tenofovir) have been shown to lead to improved prognosis in patients with HBV and decompensated cirrhosis.

While the studies examining HBV mediated decompensated cirrhosis have had different designs and have used different antivirals, the data suggest the following: 1) the oral antiviral agents all appear to be safe and effective, 2) clinical improvements in some patients have been such that some patients have been removed from liver transplant wait lists, 3) it has generally be recommended that because of the infrequency of development of resistance, entecavir and tenofovir are the best choices for treatment of patients with HBV and decompensated cirrhosis, 4) all cirrhotic patients with decompensation should be treated, regardless of HBV DNA level as early as possible, 5) oral agents (lamivudine, adefovir, entecavir, telbivudine, or tenofovir) are generally well tolerated without significant side effects. Again, while these specific studies have focused on clinical endpoints and have generally not proven that there is a reversal of fibrosis/cirrhosis, the correlation between a change in fibrosis and outcome appears to be robust.

Further evidence of the benefit of HBV antiviral agents comes from large population studies. Over the time period from 1985 to 2006, which coincided with the introduction of HBV antiviral agents, of 4793 patients with HBV cirrhosis wait listed for liver transplant, compared to, 40,923 with HCV cirrhosis, and 68,211 with neither type of viral disease, the decrease in incidence of waiting list registration was most pronounced for HBV cirrhosis⁵⁸. Further, the increase in listing for HCC associated with HBV was least dramatic. These data suggested that the widespread use of oral antiviral therapy for HBV contributed to the decreased incidence of decompensated liver disease.

Despite the remarkable results in treating HBV cirrhosis patients with oral agents, there are some patients in whom the disease is too far advanced to expect a benefit. However, the clinical variables associated with a lack of response are currently unknown. Thus, it is this author's opinion that all patients with cirrhosis should be treated.

The risk of hepatocellular carcinoma (HCC) after viral suppression

Cirrhosis appears to be the most important risk factor for development of HCC. As such, reversal of fibrosis and cirrhosis would be expected to reduce the risk of development of HCC. In a large randomized trial of patients with HBV and advanced fibrosis (Ishak stage 4

or greater) who received lamivudine or placebo, 3.9% of patients receiving lamivudine and 7.4% percent of those receiving placebo developed hepatocellular carcinoma, ($P=0.047$), suggesting that viral suppression and reversal of fibrosis can prevent the development of HCC. Other studies, including meta-analyses have suggested a similar reduction in the risk of development of HCC^{59–62}. Although the risk of development of HCC appears to be low in certain patients with viral clearance (the strongest evidence appears to be in Asian patients), this affect does not appear to be uniform. For example, in a study of entecavir for treatment of HBV including 744 total patients and 164 patients with cirrhosis, during a median follow-up of 167 weeks, 14 patients developed HCC of whom nine (64%) had cirrhosis at baseline. The 5-year cumulative incidence rate of HCC was 2.1% for non-cirrhotic and 10.9% for cirrhotic patients ($p<0.001$). Further, Caucasian patients appeared to maintain the highest HCC risk⁶³.

Summary and Recommendations

Great strides have been made in the field of HBV related fibrosis and cirrhosis. Currently, the evidence indicates that HBV viral suppression causes regression of advanced fibrosis and even cirrhosis in some patients, and therefore should be attempted in all patients with advanced fibrosis and cirrhosis. The preferred agents in patients with cirrhosis are entecavir and tenofovir, primarily because the risk of breakthrough is low. HBV viral suppression also leads to improved clinical outcomes even in patients with cirrhosis and complications (esophageal varices, ascites, hepatic encephalopathy, and coagulopathy). The risk of subsequent development of hepatocellular carcinoma is reduced after viral suppression, particularly in Asian patients, but less so in Caucasian patients. Thus, patients with HBV cirrhosis should continue to have routine screening for HCC, even after viral suppression.

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Key Points

- Robust data indicate that fibrosis regresses in patients with advanced fibrosis and even histological evidence of cirrhosis, after HBV viral suppression.
- Overall outcomes are improved in patients with HBV viral suppression, including in those with cirrhosis and complications of cirrhosis.
- The risk of subsequent development of hepatocellular carcinoma is reduced after viral suppression.
- Despite viral suppression, there appears to be some risk of future development of complications such as portal hypertension and/or hepatocellular carcinoma; the latter most commonly in patients with cirrhosis.

Box 1. Critical issues associated with HBV suppression/eradication

- How much fibrosis regression might be expected?
- Does it matter which antiviral agent is used?
- How long should the antiviral be used?
- How should fibrosis regression be measured?
- Does fibrosis reversion have an effect on clinical features of cirrhosis (such as QOL, synthetic function, portal hypertension)?
- After viral suppression, what is the hepatocellular carcinoma risk?

Figure 1.

Histological reversal of fibrosis. An example of reversal of HBV cirrhosis is shown. In (a) and (b) is shown a liver biopsy prior to lamivudine treatment. In (c), after treatment with lamivudine, liver biopsy was repeated, and reveals almost complete dissolution of fibrosis. Data similar to this have been found in patients with autoimmune liver disease, alcoholic hepatitis, hepatitis C, and others. From Wanless IR, Nakashima E, Sherman M. *Arch Pathol Lab Med* 124:1599–1607, 2000, with permission.

Figure 2.

Reversal of organ fibrosis. Fibrosis is remarkably plastic. In many, though not all, instances, tissue fibrosis can be reversed as extracellular matrix proteins are degraded. Often, removal of the inciting stimulus is sufficient, and in a few instances, therapeutic interventions targeting the underlying disease process contribute, as well. From Don C Rockey, P Darwin Bell, and Joseph A Hill. Fibrosis – A Common Pathway to Organ Injury and Failure. *N Engl J Med* 372:1138–1149, 2015, with permission.

Figure 3.

Stellate cell activation. A key pathogenic feature underlying liver fibrosis and cirrhosis is activation of hepatic stellate cells (note that activation of other effector cells is likely to parallel that of stellate cells). The activation process is complex, both in terms of the events that induce activation and the effects of activation. Multiple and varied stimuli participate in the induction and maintenance of activation, including, but not limited to cytokines, peptides, and the extracellular matrix itself. Phenotypic features of activation include production of extracellular matrix, loss of retinoids, proliferation, upregulation of smooth muscle proteins, secretion of peptides and cytokines (with autocrine effects on stellate cells and paracrine effects on other cells such as leukocytes and malignant cells – see Figure 4), and upregulation of various cytokine and peptide receptors. Additionally, evidence indicates that stellate cells exhibit several cell fates that are likely to play a critical role in fibrosis regression, highlighted at the bottom of the figure. From Rockey DC. Hepatic Fibrosis. In *Yamada's Textbook of Gastroenterology*, Wiley and Sons, Ltd. West Sussex, UK. 2016, with permission.

Figure 4.

The cellular response to wound healing. Most forms of liver injury result in hepatocyte injury, followed by inflammation, leading to activation of HSCs. Inflammatory effectors are multiple and include T cells, NK and NKT cells as well as Kupffer cells. These cells produce growth factors, cytokines, and chemokines that play an important role in stellate cell activation. Additionally, injury leads to disruption of the normal cellular environment, and also to stellate cell activation. Once activated, stellate cells themselves produce a variety of compounds, including growth factors, cytokines, chemokines, and vasoactive peptides. These substances have pleiotrophic effects in the local environment, including autocrine effects on stellate cells themselves. ECM synthesis, as well as production of matrix degrading enzymes are major consequences of stellate cell activation. From Rockey DC. Hepatic Fibrosis. In *Yamada's Textbook of Gastroenterology*, Wiley and Sons, Ltd. West Sussex, UK. 2016, with permission.

Figure 5.

The cellular mechanism of fibrosis reversion is linked to stellate cell phenotype. Activated hepatic stellate cells are removed from the fibrogenic milieu during fibrosis regression. The mechanism for their removal appears to be via their complete elimination (i.e. via apoptosis) or via reversion from an activated to a quiescent phenotype. From Rockey DC. Hepatic Fibrosis. In *Yamada's Textbook of Gastroenterology*, Wiley and Sons, Ltd. West Sussex, UK. 2016, with permission.

Figure 6. Kaplan–Meier estimate of time to disease progression. Patients were randomized to treatment with placebo or lamivudine, and followed for 36 months. Disease progression was defined as the development of hepatocellular carcinoma, spontaneous bacterial peritonitis, bleeding gastroesophageal varices, or had death related to liver disease. From Yun-Fan Liaw, Joseph J.Y. Sung, Wan Cheng Chow, et al. Lamivudine for Patients with Chronic Hepatitis B and Advanced Liver Disease. *N Engl J Med* 351:1521–1531, 2004, with permission.

Figure 7.

Histology results over 5-year treatment phase. The Ishak stage (0 to 6) of fibrosis in paired liver biopsy specimens from 348 patients at baseline, at 1 year, and at 5 years of treatment with tenofovir is shown (344 patients had specimens at all 3 time points). From Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *The Lancet* 381: 468–75, 2013, with permission.

Table 1.

Effect of antiviral treatment on HBV advanced fibrosis/cirrhosis reversion

Agent	N (patients)	Fibrosis reversion (%)	Time	Ref
Lamivudine	30	67%	3 years	41
	24	46%	3 years	42
	47	49%	1 year	45
Adefovir	12	58%	5 years	43
	15	60%	5 years	44
Entecavir	97	57–59%	1 year	45
	13	85%	3 years	47
	10	100%	5 years	46
Tenofovir	96	74%	5 years	17