

# Can Liver Fibrosis Be Reversed? Still A Widely Debated Topic

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Cirrhosis is a result of late stage scarring in chronic liver disease. Cirrhosis occurs as a result of progressive damage to the liver tissue starting with subendothelial or pericentral fibrosis (hepatic fibrosis) and progresses to panlobular fibrosis with nodule formation (cirrhosis). Up until now it has been generally thought that once fibrosis is established it is irreversible. Until recently the clinical diagnosis of cirrhosis was made based upon the signs and symptoms of end stage liver disease. Such symptoms include variceal bleeding, jaundice, ascites, muscle wasting and encephalopathy. Clinically these symptoms continue to indicate a poor prognosis in the absence of liver transplantation and are used to classify severity for patients waiting transplantation. However, due to advances in the management of liver disease and the impact that hepatitis C disease management is having, liver biopsies have led to fibrosis and cirrhosis being diagnosed at an earlier stage. It has been demonstrated in some studies that early stage fibrosis, and even advanced cases of cirrhosis can regress during treatment of hepatitis C even without the benefit of a sustained virological response (SVR) to treatment with interferon.

Basically, treatment gives the liver a vacation or rest from inflammation caused by HCV. Providing that the cirrhosis is not at such an advanced stage that treatment is not an option, treatment is often used to improve the health of the liver even if the disease cannot be eradicated.

In February 2001 issue of the *New England Journal of Medicine*, Hammel et al discussed a group of patients with liver fibrosis who had surgery to decompress an obstructed biliary system. In this patient population, some patients had their liver fibrosis regress significantly after decompression, which was confirmed by pre and post liver biopsy. Until this publication the natural history of histologic changes after biliary decompression had not been discussed in humans. This study certainly implies that fibrosis caused by biliary obstruction is reversible in some cases, but studies similar to this one need to duplicate results to rule out variations in sampling on liver biopsy. As well, this study was criticized for not having a control arm or strict selection criteria. Regardless of the criticism, the apparent improvement in fibrosis after biliary decompression adds another example to a growing list of specific interventions, which result in histologic improvements including fibrosis regression.

There have been consistent reports on the reversibility of liver fibrosis in humans when the cause of the underlying liver disease is eliminated. These include abstinence from alcohol, surgical reversal of jejunoileal (removal of a portion of the small intestine) bypass, immunosuppressive therapy for autoimmune hepatitis, long term treatment with lamivudine for chronic hepatitis B, treatment of hepatitis C and hepatitis D with interferon and, finally, treatment of primary biliary cirrhosis with methotrexate plus ursodiol.

Over the past decade or so there has been major progress in understanding the cellular and molecular regulation of hepatic fibrosis. It has been determined that the build up of scarring in fibrotic diseases of the liver is not static or a unidirectional event but a dynamic and regulated process that works well with intervention.

The growing amounts of clinical and scientific data provide us with the knowledge that extensive fibrosis or cirrhosis in patients that still have compensated liver function should no longer be considered untreatable. Both currently available as well as future therapies have the potential for preventing the progression of disease by regression of fibrosis.

Despite growing knowledge on whether liver fibrosis is reversible, there are still some unanswered questions. Liver fibrosis does not develop at the same rate in all patients and the fibrotic responses to therapy will vary from patient to patient. What are the host or disease specific factors that are linked to both a slower progression of fibrosis and a positive response to

treatment? In addition, should treatment strategies be better designed to reverse fibrosis and improve liver health, rather than to only treat when there's a good probability of a cure? For example, long-term therapy with alpha interferon may improve fibrosis in patients with chronic hepatitis C even in those patients who do not experience a virologic response. With that finding wouldn't long-term alpha interferon therapy be well justified in patients that do not gain a virologic response to treatment? It certainly seems to make a case for physicians to partner with patients to make these important treatment decisions.

**We would like to hear from our readers. The perfect scenario would be elimination of HCV and improved liver health. In the absence of both, would you prefer viral elimination or improved liver histology? Please email your comments to [sfhepcat@pacbell.net](mailto:sfhepcat@pacbell.net) Thank you.**