

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Halt and Reversal of Fibrosis

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G&H Could you describe the pathophysiology of fibrosis as it relates to hepatitis and other hepatobiliary diseases?

DR Our current understanding of fibrosis centers around injury and inflammation. For example, in patients with hepatitis C, the virus causes damage to hepatocytes and triggers a process resulting in recruitment of inflammatory cells, cytokines, and other components, which in turn activate effector cells in the liver. The predominant effector cell is thought to be the hepatic stellate cell. Stellate cells produce matrix, leading to fibrosis. In addition, other effector cells are most likely activated, including portal fibroblasts and cells derived from bone marrow, which may also contribute to the production of matrix and fibrosis.

G&H How does elimination of the primary disease state affect the progression of fibrosis? Does the body have natural pathways to reverse the fibrotic process?

DR In many patients, particularly those with hepatitis B or hepatitis C virus infection, the primary goal of treatment is to eradicate the virus and halt the chain of events that leads to inflammation and activation of effector cells. If this goal can be attained, the liver can naturally resorb fibrosis at the cellular level (Figure 1). Once the effector cells are deactivated, matrix metalloprotease enzymes will actively degrade the matrix. However, in patients with extensive scarring and cross-linking of collagen, this process may not take place and fibrosis may not be reversible.

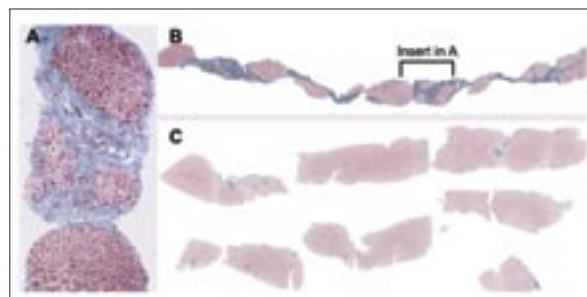


Figure 1. Reversal of fibrosis in a hepatitis B patient after viral eradication with lamivudine.

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G&H Is there anything in terms of diet and lifestyle changes that patients can do to facilitate the reversal process after their virus has been eradicated?

DR There is not much that the patient can do to actively promote reversal. They can create a favorable environment that discourages fibrotic progression by watching their diet, abstaining from alcohol, and maintaining a healthy weight.

G&H What medical therapies have been studied to promote the reversal of fibrosis?

DR The published studies thus far have been of relatively small trials. Several have examined vitamin E and milk thistle. The anti-inflammatory agent colchicine has generated considerable interest but trial results thus far have been mixed. A Veterans Affairs Cooperative study has examined the antioxidant polyenylphosphatidylcholine in alcoholic liver disease but did not show promising results.

Currently, several large, randomized, multicenter trials are ongoing to examine novel agents that have been studied in preclinical, cell-culture models. The observed mechanisms and rationale for efficacy of these agents seem promising but until we have data in humans, it's difficult to say whether these new compounds will be useful.

G&H How do you envision these medications being used in future practice?

DR It will be several years before any of these agents are used regularly in clinical practice. However, once they are available, I envision the following.

Patients will continue to receive standard antiviral therapy for their primary disease, combination pegylated interferon and ribavirin for hepatitis C and lamivudine or adefovir for hepatitis B. If they respond and their virus is eradicated, they will, for the most part, have good prognosis and will probably not require an antifibrotic therapy.

However, if these patients fail antiviral therapy, they would likely benefit from long-term antifibrotic treatment. In patients with active disease, I suspect that the best we can hope for is to halt the progression of fibrosis. To be able to reverse fibrosis in these patients would be optimal but may not be possible. Our primary goal would be to avoid progression to cirrhotic lesions and the need for transplantation. Another possible scenario is that when patients present with hepatitis B or C, they can receive

both antiviral and antifibrotic therapy simultaneously to treat the primary injury and attempt to reverse ongoing damage, respectively.

Ultimately, we will enter an era of polypharmacy in the treatment of liver fibrosis. In other chronic disease states, like hypertension and heart failure, different drugs with different mechanisms are administered to attack the problem from several directions at once. Our hope, with ongoing research, is that we will one day have a similar armamentarium to control chronic liver disease.

Suggested Reading

Rockey DC. Antifibrotic therapy in chronic liver disease. *Clin Gastroenterol Hepatol.* 2005;3:95-107.

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Lieber CS, Weiss DG, Groszmann R, et al. Veterans Affairs Cooperative Study of polyenylphosphatidylcholine in alcoholic liver disease. *Alcohol Clin Exp Res.* 2003;27:1765-1772.

Morgan TR, Weiss DG, Nemchausky B, et al. Colchicine treatment of alcoholic cirrhosis: a randomized, placebo-controlled clinical trial of patient survival. *Gastroenterology.* 2005;128:882-890.