# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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## Regression of Fibrosis Following Hepatitis C Eradication

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**G&H** Which patients are most likely to experience fibrosis regression following the eradication of hepatitis C?

**SF** One of the many benefits of developing effective, well-tolerated cures for hepatitis C has been the recognition that fibrosis can regress once the virus is cleared. This demonstrates that the liver has endogenous pathways for repair and reconstitution of its architecture once viral infection in hepatocytes is cleared. No one has quantitatively measured the rates of regression or the mechanisms underlying regression in patients who are cured of hepatitis C. However, as a general rule, patients with less fibrosis are more likely to regress or resolve their scar, even possibly in patients with cirrhosis. We do not know what is the "point of no return," after which the fibrosis is so extensive that scarring persists even when hepatitis C is cured. The best evidence, based upon clinical experience, suggests that regression of fibrosis is much less likely once patients already have portal hypertension and distortion of the hepatic architecture with portosystemic shunting.

**G&H** Is complete reversal of fibrosis possible after hepatitis C cure?

**SF** Yes, and the less extensive the fibrosis, the more likely complete reversal is. This appears to be the case for nearly all patients who are not yet cirrhotic. Thus, patients who are cured of hepatitis C and are not yet cirrhotic should have every expectation that their liver scarring will regress and, in many cases, resolve completely.

However, it is unknown whether complete regression of scarring eliminates the risk of hepatocellular carcinoma. There is reason for optimism because patients with less advanced fibrosis who achieve hepatitis C cure are at greatly reduced risk for hepatocellular carcinoma. The guidelines for screening patients for late-appearing hepatocellular carcinoma after hepatitis C cure are a little uncertain, but most clinicians agree that screening is not always mandated for patients who have minimal or modest fibrosis at the time of hepatitis C cure. In contrast, patients who have very advanced fibrosis or cirrhosis at the time of hepatitis C cure should continue to be monitored with regular ultrasound or other imaging modalities according to American Association for the Study of Liver Diseases or European Association for the Study of the Liver guidelines; this enables small hepatocellular carcinomas to be detected early and cured using ablation or resection.

**G&H** How quickly does fibrosis regression typically occur?

**SF** Because it is not clinically indicated to perform follow-up biopsies to assess fibrosis regression following hepatitis C cure, there are very limited data on the likelihood, speed, and mechanisms of fibrosis regression in this population. Having said that, data have clearly shown that complete reversal should be expected within 3 to 5 years if the patient was not cirrhotic at the time of hepatitis C cure. The more fibrosis there is at the time of hepatitis C cure, the longer it takes to regress.

**G&H** Does the treatment used to eradicate hepatitis C affect the regression of fibrosis?

**SF** There is no indication that the specific drugs used to cure hepatitis C are linked to the likelihood of fibrosis

regression. Certainly, among the different direct-acting antiviral oral medications currently available, there is no evidence that one regimen is more effective at reducing fibrosis than another.

More interesting is whether interferon-based regimens, which were used before direct-acting antiviral agents were available, are more or less likely to regress fibrosis. To my knowledge, there is no evidence that interferon-based regimens have a different rate or likelihood of fibrosis regression, assuming that they effect long-term cure of hepatitis C like direct-acting antiviral agents. However, it should be noted that interferon-based therapies are rarely used anymore, except in some patients with hepatitis B and hepatitis delta. Interestingly, older case series have shown that effective therapy for hepatitis delta using interferon-based regimens can also lead to a significant reduction in fibrosis, indicating that fibrosis regression is not unique to patients who have achieved hepatitis C cure. The general rule is that fibrosis can regress whenever the underlying cause of damage to hepatocytes is attenuated, whether through elimination or suppression of viral infection, drug toxicity, or metabolic diseases, including alcohol-associated liver disease or nonalcoholic fatty liver disease.

**G&H** Do any other factors influence the reversal of fibrosis?

**SF** Patients can occasionally continue to experience progression of liver disease despite being cured of hepatitis C. The reason for this is not clear. It has been speculated that patients still have an immune reaction generated by viral infection that persists after viral cure. An equally likely possibility is that they also have underlying nonalcoholic fatty liver disease, alcohol-associated liver disease, or possibly even rarer forms of liver disease that were not detected because it was assumed that all of their liver problems were attributable to hepatitis C. Treatment of hepatitis C can unmask concurrent causes of liver injury and fibrosis that do not necessarily improve by curing hepatitis C. Thus, a key factor that can influence regression is whether there is concurrent liver damage from another source, with the two most likely culprits being alcohol-associated liver disease and nonalcoholic fatty liver disease.

**G&H** What are the underlying mechanisms of fibrosis regression following hepatitis C eradication?

**SF** I have been involved in studies on the pathophysiology and molecular basis of fibrosis for more than 30 years, but the mechanisms of fibrosis regression have been largely ignored over the past 20 years. We know that there is an increase in matrix- or scar-degrading activity as fibrosis regresses. That enhanced protease activity can be a result of increased expression of proteases and/or decreased expression of specialized inhibitors that prevent them from degrading scar.

The exact nature of the enzyme(s) that degrade scar when fibrosis regresses after hepatitis C cure is still unclear, as are which cells are responsible for increasing the proteases and decreasing the inhibitors. There is still much to learn about the basis for fibrosis regression after hepatitis C cure. This question is important because tapping into the mechanisms that drive scar regression might allow for the identification of new therapeutic targets that can accelerate or amplify the native response of the liver in regressing scar by either activating or administering additional proteases or preventing their inhibitors from blocking their activity. Thus, understanding the cellular and molecular basis for fibrosis regression is an urgent unmet need. My laboratory and others are attacking this issue, so progress is expected in the next several years. The development of exciting new experimental tools such as single cell sequencing and single cell proteogenomics may help address this issue in experimental models, as well as in human tissues.

As mentioned, biopsies are not routinely performed when patients experience regression of fibrosis because of the invasive nature of these procedures and the fact that findings would not influence treatment in most cases. However, as there is improvement in the methods to quantify and understand fibrosis regression using noninvasive methods instead of biopsy, it will become appealing to use those noninvasive tests to better understand fibrosis regression after hepatitis C cure.

**G&H** How can the reversal of fibrosis be best monitored and measured?

**SF** The most important consequence of fibrosis reversal is clinical improvement, especially if the disease was advanced at the time of hepatitis C cure. Clinical improvement can be measured as a rise in platelet count or serum albumin, reduction in elevation or normalization of aspartate aminotransferase and alanine aminotransferase, and improvement in other blood tests of liver function, including international normalized ratio.

Increasingly, noninvasive methods are being used to track changes in the liver's amount of fibrosis through measures of liver stiffness in addition to function. These noninvasive tests include FibroScan (Echosens), which is a bedside test that measures liver stiffness, magnetic resonance elastography, corrected T1-weighted imaging, and biochemical tests that measure circulating protease

activity. Thus, a number of new technologies are emerging to assess fibrosis regression without requiring liver biopsy. These tools will yield more information to indicate how quickly and completely fibrosis can regress after hepatitis C cure.

### G&H Following hepatitis C cure, should any agents or therapeutic strategies be used to help promote the regression of fibrosis?

**SF** For patients who do not have cirrhosis, and instead have intermediate fibrosis stages F1 to F3, there is probably no reason to consider antifibrotic drugs once they are available; their fibrosis will eventually resolve as the liver structure returns to normal. Less certain is what should be done in patients who have cirrhosis at the time that their hepatitis C is cured. Antifibrotic treatments likely would not be indicated initially because it would be appropriate to first determine how much regression is occurring spontaneously after cure, which requires waiting at least a year or two. If there is evidence that there is still no regression, particularly if the patient has portal hypertension, then this might be the time for antifibrotic treatment to hasten further degradation of scar or matrix; however, such treatment is not yet available.

### G&H Which clinical outcomes improve with the reversal of fibrosis following hepatitis C eradication?

**SF** In patients who have long-term cure of hepatitis C, the risk of any clinical event is dramatically reduced, depending upon their initial stage of fibrosis. As mentioned, the risk of hepatocellular carcinoma decreases substantially, depending upon the initial fibrosis stage at the time of cure. However, the measurement of liver function is more important than just the measurement of the amount of scar. Normalization of liver function tests and reduction in liver stiffness are promising indications that liver disease will not become advanced and the patient will not die of it.

It is worth emphasizing that the liver is unique in its ability to regenerate. Although other tissues have some regenerative potential, no other organ has the capacity to completely restore full structure and function after cure of disease. This is particularly important because the regenerative capacity of the liver allows the organ to continue to function for decades despite chronic hepatitis C infection, before cure can be achieved.

### G&H What are the priorities of research?

**SF** It is vital to better understand the molecular and cellular basis of fibrosis regression in order to harness the activities that the liver naturally engages to regress scarring. These activities could translate into novel therapeutic targets and new treatments to regress scarring. I believe that we can achieve this; it will not be easy and will take time, but it will happen.

***Disclosures***

*Dr Friedman has performed consulting activities for 89bio, Agomab, Axcella Health, Blade Therapeutics, Can-Fite BioPharma, Escient Pharmaceuticals, Fate Therapeutics, Fibrocor, Forbion, Galmed, Gordian Biotechnology, Glycotest, Glympse Bio, HepGene, Insitro, Korro Bio, Merck, Metrea (Foresite), Morphic Therapeutic, NorthSea Therapeutics, Novartis, Ochre Bio, Pfizer, ProSciento Research, Resolution Therapeutics, Satellite Bio, Scholar Rock, Surrozen, and Yaqrit. He has had stock options (all <1% of company value) for Blade Therapeutics, Escient Pharmaceuticals, Galectin, Galmed, Genfit, Glympse Bio, HepGene, LifeMax, Metacrine, Morphic Therapeutic, Nimbus, NorthSea Therapeutics, Satellite Bio, Scholar Rock, and Surrozen. He has owned stock in Intercept, Madrigal, and Group K. He has performed research activities for Morphic Therapeutic (contract studies), Novo Nordisk (contract studies), Abalone Bio (SBIR grant), Galmed (contract studies), Cincera Therapeutics (contract studies), and Pionyr.*

## Suggested Reading


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