

The Treatment of Hepatic Fibrosis: Reversal of the Underlying Disease Process

Luis Servin-Abad, MD, Eugene R. Schiff, MD

Dr. Servin-Abad is a liver transplant fellow and Dr. Schiff is Professor of Medicine, both in the Division of Hepatology at the Center for Liver Diseases, University of Miami Leonard M. Miller School of Medicine, Miami, Fla.

Address correspondence to:

Luis Servin-Abad, MD, Liver Transplantation Fellow, Division of Hepatology, University of Miami Leonard M. Miller School of Medicine, 1500 NW 12th Avenue, Suite 1101, Miami, FL 33136; Tel: 305-243-4615; Fax: 305-243-3877; E-mail: servin7211@hotmail.com.

Abstract: Cirrhosis is considered an irreversible end stage of all liver diseases. Current knowledge indicates that fibrosis is part of the liver repair process, which is dynamic. Understanding this repair process will provide better approaches to halt, ameliorate, or reverse fibrosis. The diagnosis of cirrhosis is currently established by liver biopsy and in most advanced cases can be confirmed by imaging. Liver biopsy remains the gold standard but has several limitations: sampling error, size of the biopsy, and both inter- and intra-observer inconsistencies. Hence, many patients can be inaccurately staged for the degree of fibrosis on their initial biopsy, as well as on subsequent re-examination. Although a decrease of 1 stage between consecutive biopsies may be a result of sampling error, the reduction from cirrhosis by at least 2 stages more likely represents a reversal of cirrhosis. There are several cases of reversal of cirrhosis reported in association with different liver diseases. The resolution of fibrosis in the majority of these diseases is related to successful treatment of the underlying etiology (eg, hepatitis B, hepatitis C, iron overload, Wilson disease, alcohol abstinence, metabolic syndrome in fatty liver disease, and decompression of biliary obstruction). The other important feature of reversal of cirrhosis is the successful control of inflammation (eg, autoimmune hepatitis, primary biliary cirrhosis, hepatitis B, C, and D).

One of the most controversial topics in hepatology today is the regression of fibrosis and reversal of cirrhosis. The development of antifibrotic therapies that might arrest or reverse fibrosis and cirrhosis has long been pursued. This therapeutic approach might achieve disease management by targeting the complications of cirrhosis rather than curing the underlying disease.

Cirrhosis is considered the irreversible end stage of all liver diseases. Today we know that fibrosis, the precursor to cirrhosis, is part of the dynamic liver repair process, which is very closely linked to liver regeneration.

This is not a new topic. It was first alluded to in the classical Greek myth of Prometheus, whose liver was eaten by an eagle

Keywords

Cirrhosis reversal, fibrosis regression, hepatitis, nonalcoholic steatohepatitis, biliary obstruction

during the day but regenerated overnight. In 1979, Perez-Tamayo¹ published a review entitled “Cirrhosis of the liver: a reversible disease.” He presented multiple hypotheses that hold true today and described the first cases of reversal of cirrhosis.

Research Methods

In preparing this paper, a PubMed literature search was performed using the keywords “fibrosis reversal,” “cirrhosis reversal,” and the various liver diseases. Additional references were obtained from the bibliographies of the identified articles and from personal expertise. The articles included all trials and case reports of patients that initially had cirrhosis or advanced fibrosis and later had documented histologic improvement of their fibrosis.

Extracellular Production and Degradation

Years before the discovery of the key interstitial liver events, it was known that cirrhosis was sometimes reversible, as with cardiac cirrhosis. However, a more definitive understanding of the cells involved in the repair process has now emerged.

Normal liver cells include hepatocytes, endothelial cells, macrophages (Kupffer cells), and stellate cells. The stellate cell is also known as the Ito cell, lipocyte, perisinusoidal cell, or fat-storing cell, and is the principal cell related to fibrosis. Beneath the endothelial cells is the space of Disse, which separates hepatocytes from the sinusoid. This space is similar to a basement membrane, consisting of a complex matrix that allows the transport of multiple solutes and growth factors. This extracellular matrix is where fibrosis develops. The principal event in the cascade of fibrotic production is the activation of stellate cells. Activation of these cells converts them to proliferative, fibrogenic, and contractile myofibroblasts.²

When the dense collagen formed by this conversion is deposited in the space of Disse, the magnitude of fibrosis is dependent on the severity and continuity of the injury as well as multiple other factors. There are multiple enzymes that degrade the matrix in the liver, which are collectively known as matrix-metalloproteinases or matrixins. They include enzymes that are in balance with multiple inhibitors. Stellate cells are the major source of these inhibitors. During the resolution of fibrosis in the liver, one of the key events is the de-activation of the stellate cells. End results of this de-activation are either reversion or “turning off” to their initial state or apoptosis (cell death).² The understanding of this process is the basis for new strategies to control and regress fibrosis.²⁻⁴

Friedman² provides multiple strategies for antifibrotic therapy that consider the pathways of the stellate cell acti-

vation: (1) cure or control of the primary disease (hepatitis B, hepatitis C, alcoholism); (2) reduced inflammation or host response to avoid stimulating stellate cell activation (corticosteroid therapy, antagonists of tumor necrosis factor, ursodiol therapy); (3) direct downregulation of stellate cell activation (vitamin E, thiazolidinediones); (4) neutralization of proliferative, fibrogenic, or contractile responses of stellate cells; (5) stimulation of apoptosis of stellate cells (gliotoxin); or (6) increase of the degradation of scar matrix (antagonists of transforming growth factor, direct administration of metalloproteinases).

Definition of Cirrhosis

The term cirrhosis was introduced by Laennec⁵ in 1819 in his “*Traite de l’Auscultation*.” He considered liver granulations as neoformations, and because of their color he called the condition “cirrhosis” from the Greek “kirros,” meaning yellow or tawny. A working group sponsored by the World Health Organization defined cirrhosis in 1978 as a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules.⁶ Cirrhosis is not synonymous with fibrosis or widespread fibrosis. Fibrosis, by definition, is simply the appearance of connective tissue, whereas cirrhosis involves the formation of septal fibrosis between portal and/or central areas with nodular parenchymal regeneration resulting in distorted architecture.

Cirrhosis is more than a morphologic distortion of the liver architecture. It involves multiple functional abnormalities. One of the most important is the development of vascular shunts. When the underlying liver disease produces injury to the parenchyma; the repair mechanism of these areas may finish with new connective tissue and new vessels inside these areas. The vessels may connect portal with portal areas, central with central areas, or portal with central areas. These last connections are the most important because they bypass blood from the lobular parenchyma without functionally contacting metabolically active cells.⁷⁻⁹

Diagnosis of Cirrhosis

Though multiple techniques exist for the quantification of liver fibrosis, for the diagnosis of cirrhosis, clinicians rely mainly on two methods: liver biopsy and imaging to show a nodular surface that denotes a biochemical pattern of cirrhosis. Neither method is ideal and each has limitations.

Liver biopsy limitations include sampling error, size, imperfection, and inadequate interpretation of the semiquantitative scoring systems, as well as difficulty recognizing fully developed cirrhosis. Sampling error is a

well-described phenomenon as liver disease is not always homogenous in the whole organ. Taking a liver biopsy is equivalent to 1/50,000 of the liver mass, which represents a small sample subject to error.¹⁰⁻¹³ The biopsy needle size also needs to be appropriate for an adequate diagnosis, at least 2.5 cm long.¹⁴ The diagnosis of macronodular cirrhosis by needle biopsy specimen is far more difficult than that of micronodular cirrhosis. A pathologist may read the biopsy in these cases as one stage before cirrhosis (F3 in Metavir, where the maximal staging is F4). In these cases, other instruments that may help in accurately staging are the macroscopic aspect of the liver during laparoscopy or ultrasound appearance. The Ishak scoring system is a little more precise in this regard¹⁵ in establishing a biopsy as F5 (precirrhotic) or F6 (cirrhosis), with definite pathological evidence of cirrhosis. This classification in part recognizes the problematic grey zone in diagnosing cirrhosis.

Imaging can confuse cirrhosis, in some cases, with other liver diseases without fibrosis, such as diffuse nodular hyperplasia. It may also fail to detect cases of cirrhosis with a relatively smooth surface.

The second question after diagnosing cirrhosis is one of how to monitor the degree of fibrosis in these patients. The fibrosis assessment by other methods including biochemical indices of regular liver chemistries or advanced measurements of different components of the connective matrix are not specific enough to define the precise stage of fibrosis. One device that might prove useful in this regard is Fibroscan (Echosens, Paris, France), which calculates a numeric score for the elasticity or stiffness of the liver tissue that correlates with the degree of fibrosis. However, Fibroscan requires further study for validation. Thus our gold standard remains liver biopsy with the rule that a one-stage change may result from sampling error but a two-stage downgrading is likely to be significant.^{16,17}

Reversibility or Regression?

The idea that a completely cirrhotic liver can revert to a normal architecture is difficult to accept. Not all patterns of fibrosis are the same. It is possible that perisinusoidal fibrosis is more reversible than septal fibrosis.¹⁸

Even though there are multiple cases reported in the literature of reversal of cirrhosis, it is important to discuss what this means. Serial liver biopsies suggesting that a patient decreased from stage 4 to stage 2 may be a reflection of sampling error. As discussed above, the diagnosis of macronodular cirrhosis is particularly difficult on needle biopsy specimens due to the size of these nodules.¹⁹ If we consider that the involution of cirrhosis involves reverting from micronodular cirrhosis to macronodular cirrhosis and then to incomplete septal fibrosis, each stage should be diagnosed precisely.^{20,21} Even when

fibrosis disappears, some of the vascular abnormalities persist (lined by markers of CD34+ endothelial cells).¹⁸ These new vessels continue bypassing the blood from the portal areas to the central veins without making contact with the hepatocytes.

Reversal of cirrhosis implies the idea of complete disappearance of the cirrhosis with return to normal liver architecture. This never happens. Instead, fibrosis regression means that the fibrotic content is less than before; and this is probably a more appropriate term.

Experience in Specific Diseases

There are multiple examples in animals of reversal of cirrhosis. The best animal experiments had been conducted in cirrhosis induced with toxins like carbon tetrachloride.^{1,22-24} However, there are additional examples of human cases published demonstrating reversal of cirrhosis.

Autoimmune Hepatitis

Dufour and associates²⁵ described 8 patients with autoimmune hepatitis and cirrhosis or extensive fibrosis on initial biopsy. These patients were treated with corticosteroids and later additional immunosuppressants (eg, mercaptopurine or azathioprine). They had clinical improvements in biochemical parameters including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and albumin levels. The biopsies were repeated at a median interval of 47 months and showed a marked improvement with a decrease in the median Knodell score from 14.0 to 1.3, as well as a decrease in the median fibrosis score from 3.3 to 0.8. See Figure 1.

One case of overlap of autoimmune hepatitis with primary biliary cirrhosis has been described with major improvement, according to initial biopsies consistent with stage III and IV for primary biliary cirrhosis and 8 years later with a biopsy described close to normal in terms of inflammation and fibrosis.²⁶ The most efficacious therapy utilized in this case was prednisone.

Primary Biliary Cirrhosis

Kaplan and colleagues²⁷ presented a paper where 5 of 19 patients with primary biliary cirrhosis with precirrhotic disease responded to treatment with methotrexate. They had clinical, biochemical, and histologic improvement. Mean Knodell score decreased from 15.1 to 5.8 and mean fibrosis stage from 2.5 to 1. Larger trials with methotrexate after this publication failed to demonstrate the benefit of this therapy for primary biliary cirrhosis.²⁸⁻³¹

There is another case in the literature of biopsy-defined stage III primary biliary cirrhosis that could be defined as cirrhosis due to the presence of splenomegaly and esophageal varices, where the varices disappeared and

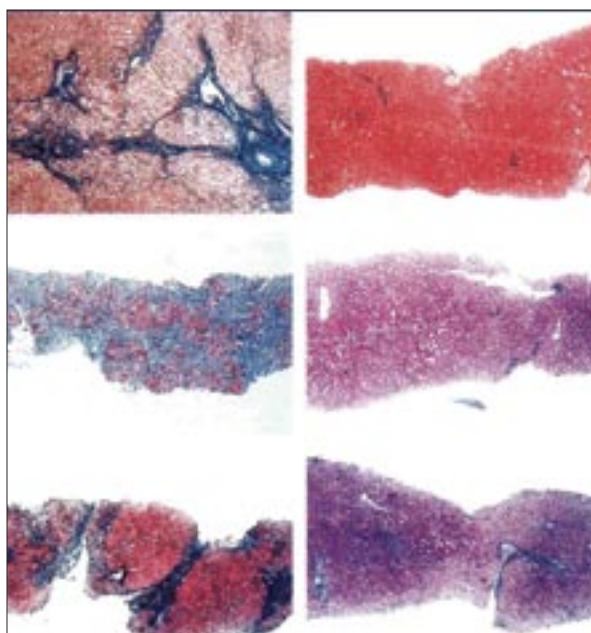


Figure 1. Reversal of fibrosis in autoimmune hepatitis patients. Histologic specimens before (left) and after (right) therapy with corticosteroids and additional immunosuppressants.

Reproduced with permission from Dufour et al.²⁵

the number of platelets increased, along with follow-up biopsy showing stage II primary biliary cirrhosis.³² In this case, though the patient was receiving methotrexate, the agent most likely involved in the regression of the cirrhosis was additional ursodiol.

Iron Overload Liver Disease

Muretto³³ presents a group of 6 patients who underwent bone marrow transplantation (BMT) for thalassemia. Liver biopsy showed cirrhosis in the majority of cases that was secondary to hemosiderosis; however there were four cases of hepatitis C virus (HCV) infection in these patients. These subjects received aggressive phlebotomy after they achieved a stable hemoglobin level with the BMT. One of them also received HCV treatment with interferon but did not achieve clearance and several also received deferoxamine. All patients improved their Ishak classification by at least 3 stages, a striking result considering their initially cirrhotic livers. In hemochromatosis there are more than 10 case reports of reversal of cirrhosis after aggressive phlebotomy achieving a negative iron balance.³⁴⁻³⁹

Copper Overload

The treatment of Wilson disease early in life has also been reported with successful management and reversal of cirrhosis. Falkmer and associates⁴⁰ described a 9-year-old girl with a finely nodular surface of the liver and a biopsy with

nodular portal cirrhosis. The diagnosis of Wilson disease was done with a low serum ceruloplasmin, increased urinary copper, and the presence of Kayser-Fleischer ring. She was treated with 1000 mg/day of penicillamine. Twenty-seven months later, she underwent another laparoscopy, demonstrating a smooth surface of the liver and almost normal architecture of the parenchyma.

Grand and Vawter⁴¹ described two other cases of Wilson disease (patients 24 and 11 years old at time of diagnosis) with reversal of cirrhosis. The patients were placed on penicillamine 1000 mg/day. Repeat biopsies (2 and 7.5 years subsequent) did not show any scarring or nodules. However, the authors stated that there was not complete restitution of the normal architecture.

The other disease associated with copper overload that has demonstrated reversal of cirrhosis is Indian childhood cirrhosis (ICC). Prand and colleagues⁴² described 30 patients with ICC treated with penicillamine 20 mg/kg/day. Mean age of the patients at diagnosis was 21.1 months. All patients had cirrhosis at the initial liver biopsy. Only 21 had a repeat biopsy done 6–60 months after the initial liver biopsy; 4 of the 21 showed almost normal histology, 5 of 21 showed incomplete fibrous septae, and 12 of 21 remained cirrhotic. Hepatic copper concentrations decreased to near normal limits. Withdrawal of the penicillamine did not cause reaccumulation of the copper or clinical deterioration as described in Wilson disease patients.

Nonalcoholic Steatohepatitis

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease in developed countries. The most severe presentation is nonalcoholic steatohepatitis (NASH), which can progress to cirrhosis. Because it is often a component of the metabolic syndrome, therapy focuses on weight reduction and control of insulin resistance.

A trial of laparoscopic adjustable gastric banding included 197 patients but only 36 with paired biopsies, the first at the time of the surgery and the second a mean of 26 months afterwards.⁴³ Of these 36 patients, 23 met the criteria for metabolic syndrome and 23 met the criteria for NASH (20 patients met both criteria). Only 1 patient with cirrhosis was included, but there were 10 with stage 3 fibrosis. Median body mass index (BMI) decreased from 47 to 34 and all metabolic parameters improved. The patient with cirrhosis had no changes in fibrosis, but of the 10 patients with stage 3 fibrosis, 7 of 10 had complete reversal of fibrosis and only 1 did not show any improvement. The median decrease in fibrosis stage in the complete cohort was 1.

More impressive was the article by Kral and associates⁴⁴ where biliopancreatic diversion was performed in 689 morbidly obese patients. Mean weight loss was 38 kilograms. All the patients showed improvement of

their metabolic syndrome and liver steatosis. Fourteen patients (2%) had cryptogenic cirrhosis with nodularity of the liver surface at the time of the operation and 11 underwent multiple repeat biopsies (8 wedge biopsies in a repeat operation and 3 needle biopsies). The biopsies were repeated at a mean interval of 41 months. Of the 8 patients with wedge biopsies, 5 had a decrease in fibrosis of 1 or more stages (fibrosis scale of 0–5), interpreted as unequivocal evidence of improvement. During the second surgical procedure, the improvement characterized by a smooth surface of the liver (previously nodular) was evident. Among the 3 patients who had needle biopsies, 2 showed improvement of the fibrosis of at least 2 stages.

One of the patients with reversal of cirrhosis had an anastomosis dismantled because of intractable diarrhea. After the procedure, the patient regained the weight and died 4 years later with cirrhosis complications.

Hepatitis B and D

The treatment of hepatitis B virus (HBV) has changed dramatically over the last 10 years. Dienstag and coworkers⁴⁵ published experience with patients who were already treated with lamivudine for one year, but did not achieve hepatitis B e antigen (HBeAg) seroconversion. Liver biopsies were performed before and after lamivudine treatment for 1 year. Patients without HBeAg seroconversion (n=63) were treated with lamivudine for 2 additional years. The median between the first and last biopsy (a third one) was 3.5 years. Of these subjects, only 8 had cirrhosis (stage 4). Of the 8 patients with cirrhosis, 5 decreased to stage 3, 2 decreased to stage 1, and 1 from 4 to 0. Although a one-stage decrease could, in many cases, be a result of sampling error, reversal in at least 3 of the 8 patients is more likely to be genuine. See Figures 2 and 3.

Hadziyannis and colleagues⁴⁶ presented the long-term experience, over 4–5 years of treatment with adefovir, in HBeAg negative patients. Paired liver biopsies were available for 46 patients. The proportion of patients who had a decrease of at least one stage in Ishak fibrosis score consistently increased over 5 continuous years: 33% at year 1, 46% at year 2, and 71% at year 5. Five of 7 patients with cirrhosis (Ishak fibrosis scores 5 or 6) had a decrease of at least 2 stages in the fibrosis score, which is consistent with reversal of cirrhosis.

Farci and associates⁴⁷ describe 36 patients co-infected with hepatitis B and D. They were treated with high-dose (9 million units) or low-dose (3 million units) interferon alfa-2 for 48 weeks. The patients were followed for a median period of 11.7 years (± 1.1), and during that time underwent 3–4 biopsies. The study included 10, 9, and 8 patients with cirrhosis in the high-dose, low-dose, and control groups, respectively. Only high-dose interferon was associated with long-term survival, biochemical improvement, and histologic improvement (in activity

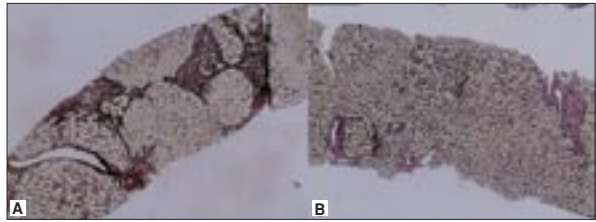


Figure 2. Improvement of bridging fibrosis during lamivudine therapy. Patient with YMDD-variant hepatitis B virus before (A) and after (B) treatment.

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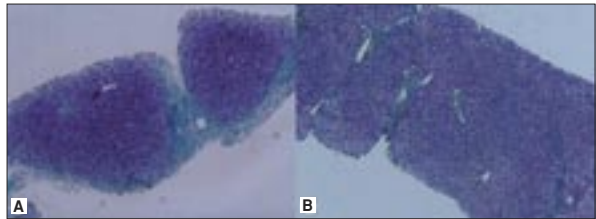


Figure 3. Improvement of cirrhosis during lamivudine therapy. Patient with wild-type hepatitis B virus before (A) and after (B) treatment.

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and fibrosis). Four patients with cirrhosis on the first 3 biopsies showed an absence of fibrosis on the last biopsy. Nonetheless, hepatitis D viremia was still detectable in all of them until the last biopsy, when 2 of 4 cleared the hepatitis D. The improvement was associated with loss of the IgM anti-HD (hepatitis D), improvement in albumin levels, and decrease in the globulin fraction. There was no significant improvement in the low-dose interferon group. There is a possibility of sampling error or the conversion from micronodular cirrhosis to macronodular cirrhosis because the first 3 biopsies had cirrhosis, but only the last one had no fibrosis. There was a simultaneous improvement of the biochemical and virologic parameters.

Similar examples of fibrosis regression and reversal of cirrhosis with nucleoside/nucleotide analogs for the treatment of HBV, when given for long periods of time with sustained suppression of viral replication, can be anticipated.

Hepatitis C

Dufour and coworkers⁴⁸ reported 2 HCV patients with reversal of cirrhosis after treatment with interferon alfa-2a. One patient was treated with 18 months of therapy and relapsed after stopping the interferon and the other with only 3 months of therapy before stopping due to severe depression, with no response of the HCV. However, both patients experienced resolution of the cirrhosis as reported.

Shiratori and associates⁴⁹ reported on 593 patients with HCV who underwent repeated liver biopsies (median interval between biopsies 3.7 years). The treated group was heterogeneous and included patients who received interferon alfa (2a, 2b, and natural interferon alfa) and interferon beta. The duration of treatment was from 2 to 6 months. There were 24, 30, and 8 patients with cirrhosis on the initial biopsy in the sustained virologic response (SVR) group, the non-SVR groups, and the untreated group, respectively. Among the untreated patients, there was no change in the cirrhosis. Among the 24 who achieved SVR, 7 decreased their level of fibrosis from F4 to F2 and 4 from F4 to F3. Among the 30 treated patients not achieving SVR, only 1 improved from F4 to F1, 1 from F4 to F2, and 7 from F4 to F3. The overall response in terms of fibrosis progression was better in the group that achieved SVR. However, in the treated group that did not achieve SVR, many patients still improved in their fibrotic scores.

Poynard and colleagues⁵⁰ unequivocally showed reversal of HCV-related cirrhosis. Their multicenter study included patients undergoing multiple regimens of regular interferon and pegylated interferon alfa-2b, with and without ribavirin. Among the entire cohort, there were 153 patients with cirrhosis (stage 4 by Metavir score). Of these, there was reversal in 75 patients (49%): 23 to stage 3, 26 to stage 2, 23 to stage 1, and 3 to stage 0. There may have been some sampling error between stages 3 and 4. However, there are cases with subsequent stage 0–2; making the reversal of cirrhosis much more likely.

Secondary Sclerosing Cholangitis

Hammel and colleagues⁵¹ presented experience of 11 patients with biliary obstruction with possible secondary sclerosing cholangitis. It included a heterogeneous group of patients, all with chronic pancreatitis with secondary biliary stenosis (10/11 secondary to alcohol, 1/11 idiopathic). Initial liver biopsies demonstrated more changes compatible with cholestatic changes than alcoholic features. All patients underwent a surgical biliary drainage. Second biopsies were performed a median of 2.5 years later. Nine of 11 patients required another operation and underwent biopsy during this procedure. The other 2 had percutaneous liver biopsies because of alcoholic liver disease. Only 1 of these patients initially had cirrhosis (grade 3, fibrosis grading from 0 to 3) and 6 of the 11 had grade 2. The patient with cirrhosis improved from grade 3 to grade 1. Overall, 2 of 11 patients improved 2 fibrosis grades, 4 of 11 improved one grade, 3 of 11 remained stable, and 2 of 11 experienced worsening fibrosis. These last 2 patients had restenosis of the biliary tree. It is difficult to assess if abstinence from alcohol played a role. Eight patients were abstinent 4 months before the procedure but 3 started drinking again.

Alcoholic Cirrhosis

The evidence for reversal of cirrhosis in alcoholic liver disease is scarce. There is a description of one patient with alcoholism and cirrhosis administered colchicine with complete reversal of the cirrhosis 24 months after the initial biopsy.¹ However there is no information regarding abstinence. This patient was part of the trial by Kersenobich and associates^{52,53} that was published at a later date.

In this trial, the effect of colchicine was assessed in a heterogeneous group of cirrhotic patients, 45 alcoholic, 41 posthepatic, and 14 from other causes.⁴⁹ There was increased survival in the colchicine group. There was no fibrosis improvement in the placebo group. Nevertheless, in the colchicine group, 9 patients had improvement in their cirrhosis. Two of 9 had normal biopsies after 18 and 42 months and 7 of 9 had minimal portal fibrosis 6–108 months after the initial biopsy. It is difficult to assess which of the patients with reversal of cirrhosis had alcohol as an etiology and whether or not they abstained. However, 45% of the initial group were alcoholics.

Morgan and associates⁴⁵ published a trial of patients with alcoholic cirrhosis with advanced disease and Child-Pugh-Turcotte B and C scores. Patients (n=549) were randomized to receive colchicine or placebo (for 2–6 years). Liver biopsy was requested at entry and 24 months after the treatment. Abstinence was assessed by interview and alcohol levels, and 69% of the population had less than 1 drink per day without any difference between the treatment and placebo groups. Colchicine did not reduce the overall or liver-specific mortality. In this study, one patient had reversal of cirrhosis after 5 years of treatment with colchicine, even though the patient continued drinking. Another 7 patients (4 in the placebo group and 3 in the colchicine group) improved to septal fibrosis (incomplete cirrhosis). The improvement in these last patients could be interpreted as sampling error.

The evidence of this trial and other studies does not support the therapeutic efficacy of colchicine.^{55,56} Improvement in fibrosis among both placebo- and colchicine-treated patients is likely to be a result of abstinence from alcohol.

Summary

There are multiple examples demonstrating reversibility of cirrhosis. The resolution of fibrosis in the majority of the diseases is related to success for treatment of the underlying etiology (eg, hepatitis B, hepatitis C, iron or copper overload, metabolic syndrome in fatty liver disease, biliary obstruction). The other important feature in reversal of cirrhosis is the control of inflammation (corticosteroids in autoimmune hepatitis and primary biliary cirrhosis, interferon in hepatitis C without SVR and in hepatitis D). In the future, with a better understanding of hepatic

fibrosis pathogenesis and better therapies for the underlying liver diseases, we may be able to ameliorate, halt, or reverse hepatic fibrosis even if there is failure to eradicate or cure the specific etiologies of liver disease.

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