HEPATITIS C: IS REGRESSION OF ADVANCED FIBROSIS POSSIBLE AFTER TREATMENT?

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ABSTRACT

Liver cirrhosis represents a severe complication for hepatitis C patients. Patients with cirrhosis require immediate treatment; a sustained virological response has been demonstrated to reduce the probability of complications and to improve the prognosis. The optimal outcome of treatment is regression, which in many cases is difficult to achieve due to histological changes. Nevertheless, cirrhosis regression has been reported in >50% of patients treated with antiviral drugs who were assessed by biopsy both before and after treatment. Similar results were obtained when transient elastography was used to estimate fibrosis stage. However, more studies with longer follow-up periods are necessary to confirm whether the decrease in liver stiffness resulting from a sustained virological response to a direct-acting antiviral is correlated with improved clinical outcomes.

Keywords: Hepatitis C, liver cirrhosis, regression fibrosis, liver biopsy, elasticity imaging techniques, therapy.

INTRODUCTION

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease worldwide. Its long-term impact ranges from minimal damage to extensive fibrosis and cirrhosis, which is sometimes accompanied by hepatocellular carcinoma (HCC).[1]

The objective of chronic hepatitis C (CHC) treatment is to achieve a sustained virological response (SVR), defined as the absence of viral replication 12 or 24 weeks after treatment completion. A SVR which is stable over time, reduces morbidity and mortality, and is considered in most cases to be equivalent to cured HCV infection.[2,3] However, complications such as HCC can emerge in patients with a SVR following treatment.[4-7] Studies are still needed to determine whether the life expectancy of these subjects is similar to that observed in the general population.[8]

Many causes of chronic liver disease, including autoimmune hepatitis, haemochromatosis, total parenteral nutrition-related cirrhosis, and primary biliary cholangitis result in cirrhosis that may regress.[9] It has been shown that in some cases, viral suppression in chronic hepatitis B, and SVR in CHC, improve fibrosis and cirrhosis,[10] however definitive data is lacking.

FROM THE NORMAL LIVER TO CIRRHOSIS

Although cirrhosis is the end-stage of every chronic liver disease, its natural history varies significantly. An asymptomatic or 'compensated' phase of cirrhosis is rapidly followed by a progressive stage that is marked by the development of portal hypertension related complications and/or liver dysfunction, called 'decompensated cirrhosis'.[11] Evidence suggests that cirrhosis is an extremely heterogeneous pathological condition that is neither static nor regularly progressive but rather dynamic and bidirectional with a wide spectrum of clinical manifestations.

The liver is organised into lobes, with blood streaming from the portal tract to the central vein throughout the hepatocyte trabecula. A normal liver contains no fibrous tissue, which is formed when repetitive injury drives an unregulated healing response, resulting in an imbalance in

the extracellular matrix and the progressive replacement of functional liver parenchyma with fibrous tissue.[8,12,13]

During the compensated stage, pre-clinical cirrhosis is defined histologically (using the METAVIR and Ishak scoring systems) as a diffuse process in which the normal anatomical lobules are replaced by architecturally abnormal nodules separated by fibrous tissue.[8,13,14] The histological progression of viral hepatopathies is characterised by the formation of fibrous tissue around the portal tract, and of fibrotic bridges between the portal tract and the nearby central vein.[14] Fibrosis is scored in stages, whereas necroinflammation is evaluated by grade. Stratification of fibrosis is defined by the amount of fibrosis and the degree of architectural disorganisation. These semiquantitative histological classifications are widely used.[13,14]

In cirrhotic patients (F4 in the METAVIR classification), functional liver tissue is replaced by fibrous tissue composed of different molecules, including highly cross-linked collagen.[13,14] Cirrhosis is characterised by annular fibrosis that is associated with architectural reorganisation, which drives a shift from lobular to nodular organisation.[12] Other commonly observed abnormalities include: angiogenesis, vascular remodelling, sinusoidal capillarisation, and perisinusoidal fibrosis. All of these processes lead to portal hypertension and, finally, liver decompensation.[13,14] Moreover, two different substages (1 and 2) have been identified based on the absence or presence of gastro-oesophageal varices, resulting in different outcomes.[8]

IS CIRRHOSIS REVERSIBLE?

Cirrhosis represents the final form of fibrosis in almost every chronic hepatopathy.[13] Until recently, fibrosis and cirrhosis were considered irreversible, and the goal of treatment was to halt the progression of these conditions.[9] It has since been demonstrated, in both animal and human models, that cirrhosis may regress or revert in some cases, but it is first necessary to eliminate the causative injury.[10,13,15,16]

Mechanisms of fibrosis have focussed on hepatic stellate cells, which become fibrogenic myofibroblasts during injury through 'activation'. Recent studies have clarified pathways of stellate cell gene regulation and epigenetics, emerging pathways of fibrosis regression through the recruitment and amplification of fibrolytic macrophages, nuanced responses of discrete inflammatory cell subsets, and the identification of the 'ductular reaction' as a marker of severe injury and repair.[17] Most of this attention has been focussed on stellate cell and myofibroblast responses given their critical roles in extracellular matrix production, yet liver injury elicits a complex multicellular response involving other resident cells, such as hepatocytes, macrophages, sinusoidal endothelium, and distinct families of infiltrating immune cells including B cells, natural killer (NK) and NK T cells, and myeloid-derived suppressor cells.[17]

Three conditions must be met for the reversion of fibrosis to occur: a) fibrous tissue must be degraded, b) fibrosis must be replaced by newly formed hepatocytes (i.e. regeneration), and c) normal lobular architecture must be restored.[13] The first condition for reversion, fibrotic septal degradation, is achieved via metalloprotease digestion.[18] Some hallmarks of evolved fibrosis, such as the presence of extensive collagen crosslinking or accumulated elastic fibres, may impair enzymatic degradation by the metalloproteases. It is therefore reasonable that recently established cirrhosis reverts more easily than long-term cirrhosis.[13] The second condition for reversion, regeneration of hepatocytes, requires the downregulation of the inflammatory response. In CHC, the inflammatory response stops when a SVR has been achieved. Both age and the number of necrosis and regeneration cycles have been implicated as factors in the regenerative capacity of hepatocytes. In atrophic cirrhosis, the capacity to regenerate hepatocytes is decreased, and cirrhosis reversion is improbable.[19] Finally, the most restrictive factor in cirrhosis regression is the ability to revert to a lobular organisation from a nodular one.[12] Portal tracts can emerge after fibrosis reabsorption, but this process is improbable in cases of portal venous or central thrombosis.

In summary, regression is more likely in cases of recent cirrhosis, controlled aetiology, and extant regenerative capacity, as well as in the absence of portal thrombosis.[13] Furthermore, in decompensated cirrhotic patients, the effect of treating fibrosis has not been yet studied; until recently, interferon (INF) treatment was the only accepted care regimen for CHC, though it is contraindicated in decompensated patients.[10] Therefore, the exact point at which cirrhosis becomes irreversible remains unknown.[8]

Table 1: Rates of cirrhosis regression measured by liver biopsy in hepatitis C virus patients who achieved sustained virological response with interferon-based therapy.

Study	Patients with cirrhosis, n	Fibrosis scoring system	Regression rates, n (percentage of total cohort, %)
Arif et al.[36]	6	Ishak	5 (83)
George et al.[5]	8	Ishak	6 (75)
Maylin et al.[38]	14	Metavir	9 (64)
Pol et al.[37]	17	Metavir	4 (24)
Shiratori et al.[34]	24	Metavir	11 (46)
Poynard et al.[35]	37	Metavir	25 (68)
D'Ambrosio et al.[39]	38	Metavir	23 (61)
Mallet et al.[4]	39	Metavir	17 (44)

HOW CAN CIRRHOSIS REGRESSION BE DEMONSTRATED?

Hepatic fibrosis stage is the principal predictor of liver disease progression and determines the treatment regimen.[20] Historically, liver biopsy has been the gold standard for staging liver fibrosis.[20] However, because it is an invasive and expensive technique that is marred by sampling error as well as intra and inter-observer variability, non-invasive methods, such as the FibroTest or transient elastography (TE), are currently preferred for patients with CHC.[21-24] Moreover, the current histological classification system was not designed to assess cirrhosis regression. Recently, the use of the Laennec classification has been proposed for this purpose, as follows: F4a: cirrhosis with macronodules and thin septa; F4b: cirrhosis with micronodules and thick septa; and F4c: atrophic cirrhosis with small nodules and large, thick fibrotic septa. The last class is least likely to regress.[25]

Currently, non-invasive methods are preferred for measuring liver fibrosis because they pose fewer risks, are better tolerated by patients, and are suitable for longitudinal study of changes in fibrosis in HCV patients.[26,27] TE is the most accurate non-invasive method for detecting cirrhosis in patients with viral hepatitis and it can be considered the non-invasive standard for the measurement of liver stiffness (LS).[28] LS is correlated with liver fibrosis and cirrhosis, as determined by liver biopsy.[27,29] Its values are strongly correlated with the METAVIR fibrosis stages. However, a substantial overlap of LS values was observed between lower fibrosis stages so TE performs better for detection of cirrhosis than for detection of significant fibrosis.[28] Thus, TE is considered a surrogate marker of fibrosis.[30,31] TE has been validated for the diagnosis of liver-related complications and has high prognostic value for predicting liver-related death and overall survival.[8,25,27,32-34] However, the use of TE is problematic in some cases; an improvement in fibrosis might be confused with a decrease in inflammation after treatment; might not appear the same in cases of obesity or ascites; and can yield false positives in cases of acute hepatitis, extrahepatic cholestasis, or hepatic congestion.[11,25,28,29,35] Despite their advantages over liver biopsy, the use of non-invasive methods to evaluate the evolution of long-term fibrosis and cirrhosis after treatment has not been sufficiently validated.[25,36]

The following section will discuss the lines of evidence supporting cirrhosis regression in some patients with CHC after treatment, including data obtained via liver biopsy and non-invasive methods such as TE.

Cirrhosis Regression Defined by Liver Biopsy

Several studies have used liver biopsy to assess the evolution of liver fibrosis after antiviral treatment of CHC with INF or pegylated interferon (PEG-INF), either with or without ribavirin (RBV). These studies have demonstrated that antiviral therapy can improve liver histology[4,5,36-44] although few cirrhotic patients have been evaluated[45] (Table 1).

In a recent meta-analysis of six studies involving 137 patients with cirrhosis who achieved a SVR following PEG-INF and RBV treatment, the

regression of cirrhosis was assessed by performing a biopsy before and after antiviral therapy.[45] The regression of cirrhosis was defined as a reduction of the METAVIR stage to ≤F3 or of the Ishak fibrosis score to ≤4. In this meta-analysis, liver biopsies obtained from patients who had achieved a SVR revealed the regression of cirrhosis in 73 cases (53%). However, the cirrhosis regression rates among the included studies varied widely, ranging from 24–83%. The authors observed that SVR led to an almost 3-fold increase in the chance of cirrhosis regression, and found that the severity of liver disease is a good predictor of antiviral response. Furthermore, regression may be less likely in patients with more advanced or established cirrhosis.

TRANSIENT ELASTOGRAPHY ASSESSMENT OF THE IMPACT OF TREATMENT AND SUSTAINED VIROLOGICAL RESPONSE ON FIBROSIS AND CIRRHOSIS

Several studies have assessed the validity of TE for evaluating longitudinal disease regression and the progression of fibrosis in patients with CHC of any genotype who were treated with PEG-INF-α and RBV.[8,31,46-54] These studies utilised different designs and treatment regimens, and follow-up periods ranged from 24 weeks[50] to 4 years.[49] Previous studies demonstrated a significant reduction in LS in treated patients compared with untreated controls,[27,29] although the use of control patients cannot currently be justified.

The most important finding in the majority of studies was the significant decrease of LS and biomarker values compared with baseline in patients with HCV who had achieved SVR after PEG-INF and RBV treatment.[8,20,36,47-54] For example, when TE is used as a marker of fibrosis, the cirrhosis regression rate appeared to be higher, ranging from 60–89% in a recent systematic review of three studies involving 56 patients.[10] The high regression rates and variability between studies warrant cautious interpretation; to date, the number of patients evaluated has been limited and different techniques for measuring fibrosis have been used, along with different cut-offs and follow-up periods.

Other studies have reported the regression of advanced fibrosis using other non-invasive markers. A large retrospective study with a 10-year mean follow-up period found that after treatment, fibrosis, as measured by the FibroTest, improved in 49% of patients with advanced baseline fibrosis who had achieved a SVR.[7]

Impact of New Antivirals on Liver Fibrosis Measured by Transient Elastography

The development of direct antiviral agents (DAAs) has increased the SVR rate in patients with HCV and has resulted in faster viral clearance than previous treatments have achieved.[55] Recently, our group used TE to evaluate fibrosis regression in patients treated with HCV protease inhibitors (PIs).[56] The authors of this paper are not aware of any other studies that have evaluated DAAs or other INF-free treatment in this manner.

This study sought to determine whether LS decreased after treatment with a first-generation PI (e.g. boceprevir or telaprevir) in conjunction with PEG-INF and RBV in patients with the HCV genotype 1. Only patients with advanced fibrosis were analysed (TE >9.5 kPa, equivalent to an F3 and F4 classification) because they had a greater risk of developing complications, thus it was imperative that they achieved SVR and decreased fibrosis.[26,56] Patients with decompensated cirrhosis were excluded.

A decrease in LS by the end of the follow-up period compared with the baseline was observed in 77% of patients overall. This decrease was equivalent to >30% of the baseline fibrosis level in almost half of cases; a somewhat higher figure of 42% was reported by Hèzode et al.[50] who used a PEG-INF and RBV treatment. After PI triple therapy, fibrosis measured by TE decreased in almost 90% of patients with a SVR (Figure 1). The decrease in LS was significantly greater in patients who had achieved a SVR (Figure 2).

In both univariate and multivariate analyses SVR alone was correlated with improved fibrosis, which was consistent with other studies.[7,50] In this study, when all other variables were held constant, SVR increased the odds of decreasing fibrosis by 18.85-fold.

An improvement in LS was also observed in some non-SVR patients.[49] This finding, which has no clear explanation, suggests an effect of treatment on fibrosis different from that of SVR. This finding has already been shown for PEG-INF and RBV treatments, which resulted in improvements in cases of relapse,[30] and, to a lesser extent, in non-responders.[31,58] This could be due to an antifibrotic effect of PEG-INF and may be unrelated to SVR.[7]

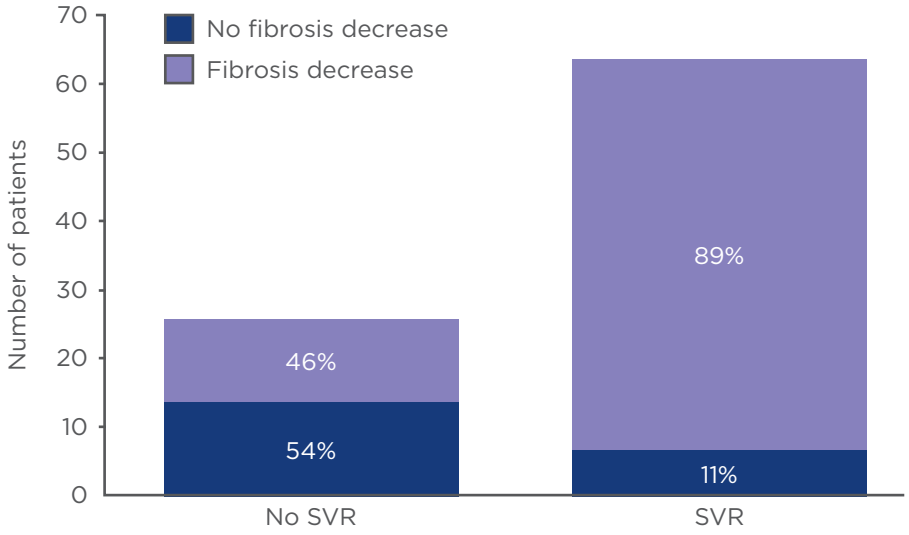

Figure 1: Number and percentage of patients with a decrease in fibrosis as measured by transient elastography in the groups with and without sustained virological response.
SVR: sustained virological response.

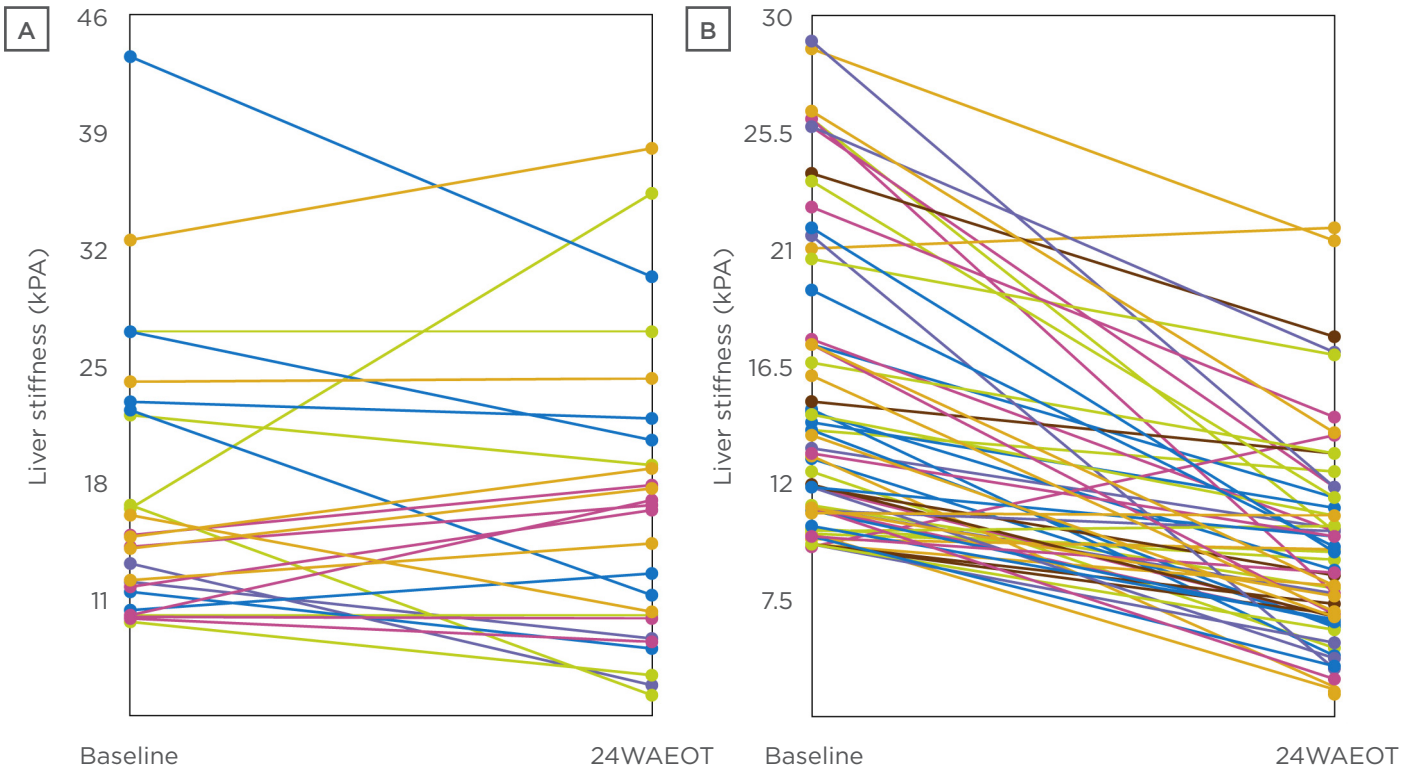

Figure 2: Individual liver stiffness changes relative to baseline at 24 weeks after treatment.
A) Patients who did not achieve sustained virological response (SVR). B) Patients who achieved SVR. Two outliers are not included in the graph.
24WAEOT: 24 weeks after the end of treatment.

In this study, LS decreased in all but one patient with cirrhosis, suggesting a decrease in fibrosis after treatment. Perhaps the most significant finding of this study was that 57% of cirrhosis patients with SVR demonstrated cirrhosis regression by TE.

WHAT IS THE CLINICAL RELEVANCE OF CIRRHOSIS REGRESSION?

SVR is considered a first step towards the reduction of future mortality in HCV-infected patients.

In cirrhotic patients, SVR improves prognosis because it reduces decompensation and the need for a liver transplant, thereby improving survival.[2,3,28]

As mentioned above, SVR is also associated with a reduction of fibrosis and the regression of cirrhosis in many patients. Nevertheless, it remains unknown whether the improvement in fibrosis is a consequence of SVR or is an independent predictive factor of a positive clinical outcome.[9] The mechanisms of hepatitis B and C treatments are different, so cirrhosis regression must be explained by different factors.[10] Current hepatitis B antiviral therapies work by chain termination thereby promoting the cessation of viral replication, but they cannot eliminate covalently closed circular DNA in the liver and even long-term treatment may not eradicate the virus, whereas DAAs against HCV may induce a virus-free state if a SVR is accomplished with only short duration of treatment.[60]

Once viral replication is suppressed in hepatitis B patients, the risk of decompensation and HCC decreases. In contrast, therapies for HCV have revolved around the use of INF, which has been limited in patients with decompensated liver disease as it results in worsening liver function.[10]

Preliminary data has shown that with the introduction of new INF-free therapies, some combinations of DAAs are indicated in decompensated cirrhosis, and involve an improvement in MELD (Model for End-stage Liver Disease) scores of ~70% only 4 weeks after treatment finalisation.[60]

Moreover, the pathogenesis of HCC is less dependent on viral replication than on the presence of cirrhosis.[10] Even in the presence of a SVR, patients with cirrhosis continue to be at risk for HCC.[10] Nowadays, patients with advanced liver disease may be treated with new INF-free antiviral treatments, for which the effects on HCC and cirrhosis regression are unknown. However, it is certain that the assessment of residual liver fibrosis in patients who achieve SVR is important for determining prognosis and for defining cost-effective surveillance programmes for liver-related complications.[42]

In decompensated HCV patients, it is still uncertain whether the severe fibrosis could be reversed to some extent. Although successful treatment outcomes in HCV-induced cirrhosis have been shown to reduce rates of HCC, it is not clear at the moment whether DAA treatment for decompensated patients confers the same benefit.[60] Some studies[7,50,56] report that LS values remained significantly higher after the SVR in patients with baseline cirrhosis compared with those without baseline cirrhosis. In addition, for reasons not yet known, advanced fibrosis and cirrhosis did not regress or progress in some patients, despite the presence of a SVR;[7,50] these patients have an increased risk of HCC compared with those in whom fibrosis had stabilised or regressed.[44] Comorbidities such as alcohol consumption, diabetes, or obesity probably play a major role in the progression of liver disease in SVR patients.[59] Screening for HCC every 6 months by ultrasound or monitoring oesophageal varices is recommended for all cirrhotic patients with an eradicated or inactive viral disease.[5,7,36]

Further investigation is needed to determine whether fibrosis amelioration and cirrhosis regression persist over a longer period of time. Data describing cirrhosis regression may play an important role in predicting long-term prognosis, assessing clinical follow-ups, and establishing the frequency of HCC screening.[10] However, more long-term studies are necessary to confirm whether the decrease in LS after achieving a SVR with DAA is correlated with improved clinical outcomes.[59]

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