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Fibrosis regression following Hepatitis C antiviral therapy

Fibrosis regression following Hepatitis C therapy

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Abstract

Hepatitis C virus (HCV) infection is one of the most common causes of liver pathology. It is a major etiological factor of continuous liver injury by triggering an uncontrolled inflammatory response, causing liver fibrosis and cirrhosis. Liver fibrosis is a dynamic process that can be reversible upon timely cessation of the injurious agent, which in cases of HCV is represented by the sustained virological response (SVR) following antiviral therapies. Direct-acting antiviral therapy has recently revolutionized HCV therapy and minimized complications. Liver fibrosis can be assessed with variable invasive and non-invasive methods, with certain limitations. Despite the broad validation of the diagnostic and prognostic value of non-invasive modalities of assessment of liver fibrosis in patients with HCV, the proper interpretation of liver stiffness measurement (LSM) in patients after SVR remains unclear. It is also still a debate whether this regression is caused by the resolution of liver injury following treatment of HCV, rather than true fibrosis regression. Regression of liver fibrosis can possess a positive impact on patient's quality of life reducing the incidence of complications. However, fibrosis regression does not abolish the risk of developing hepatocellular carcinoma, which mandates regular screening of patients with advanced fibrosis.

Key Words: Fibrosis regression; HCV; DAAs; HCC; liver fibrosis; cirrhosis

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Core Tip: Hepatitis C virus (HCV) infection is one of the most common causes of hepatitis that results in continuous liver injury. Uncontrolled inflammatory responses result in liver fibrosis and cirrhosis. Liver fibrosis is a dynamic process that can be reversible upon timely cessation of the injurious agent. In cases of HCV, achievement of sustained virological response by antiviral therapies might be accompanied by

regression of liver fibrosis and improvement of the patient's clinical profile. Assessment of liver fibrosis can be done with invasive and non-invasive methods, with certain limitations. Fibrosis regression can positively impact patients' quality of life, reducing complications.

INTRODUCTION

Hepatitis C virus (HCV) infection is a major causative agent incriminated in liver pathology. It commonly causes progressive liver disease that ranges from chronic inflammation to fibrosis and cirrhosis, with its complications including hepatocellular carcinoma (HCC). A long-term, persistent and uncontrolled inflammatory response is the hallmark of such diseases, leading to hepatic injury and more serious disease progression[1]. Chronic infection develops in around 85% of infected patients. According to the World Health Organization, about 71 million individuals worldwide are chronically infected with HCV, and mortality because of HCV-related hepatic complications approaches 0.39 million infected people annually. A major complication of HCV is liver fibrosis; and there is an ongoing need of better assessment of hepatic fibrosis with different accurate modalities[2]. Also, discovering an effective antiviral therapy was a major target for research, and fibrosis regression following treatment was a substantial challenge[3]. With the evolution of INF-free DAA has; the natural history of chronic hepatitis C has been modulated and now viral cure has become much more feasible[4].

HCV AND LIVER FIBROSIS

Following infection with HCV, the immune responses in the liver are initiated by hepatocytes, Kupffer cells, hepatic stellate cells (HSCs) and immune cells (macrophages, mast cells, dendritic cells, and natural killer cells) recruited to the liver, causing spontaneous elimination of acute HCV infection. However, failure of the immune responses to eliminate the virus is documented in 70%–80% of cases during the acute phase, leading to chronic infection[5]. HSCs respond to a variety of extracellular signals that drive the fibrogenic response. Recent single-cell RNA sequencing studies have shown remarkable variability in HSCs and identified unique markers for different HSC subtypes[6].

Persistent HCV replication in hepatocytes triggers uncontrolled inflammation and production of excessive inflammatory cytokines, which exacerbates tissue damage (1)

and stimulates the quiescent HSCs, leading to their activation and differentiation into myofibroblasts. Myofibroblasts are the main cells responsible for triggering fibrogenesis and the formation of various extracellular matrix (ECM) components in order to repair damaged tissues[7]. Because of increased cross-linking by tissue transglutaminases and resistance to proteolysis by metalloproteinases, the ensuing liver damage speeds up the thickening of septae, preventing the total regression of fibrosis. Furthermore, excessive ECM deposition leads to scar development, which may generally be corrected by fibrolysis. ECM deposition and breakdown alternate in the progression of liver fibrosis. When hepatic damage persists, fibrogenesis finally outpaces the liver's ability for scar clearance, and extracellular matrix accumulates[8]. However, liver fibrosis can be reversible following the resolution of HCV infection early. This potential reversibility decreases by the chronic persistent damage-causing fibrogenesis besides insufficient fibrinolysis even if HCV infection has resolved. At this point, fibrosis becomes irreversible and more progressive ending toward LC clearance of activated HSCs through apoptosis is a determining factor for liver fibrosis regression in chronic HCV patients[9]. Despite the remarkable efficacy of currently used direct-acting antivirals (DAAs) in eradicating HCV in over 95% of cases, this does not signify a cure from late-stage fibrosis or cirrhosis[10]. Infected individuals with HCV-associated fibrosis and viremia may need further therapy to effectively resolve liver damage caused by the virus.

FIBROSIS REGRESSION FOLLOWING HCV TREATMENT: DOES FIBROSIS REALLY REGRESS?

The exact definition of fibrosis regression has not been properly established, but it shows a reduction in fibrosis content. However, this definition does not consider the other changes in liver architecture, including changes in nodule size, the extent of terminal venular collapse, elements of regeneration, or altered types or distributions of collagen and other ECM components, especially in cirrhotic liver. Neither is there a standardized definition of “clinically significant fibrosis regression.” However, it is proposed that the concept is most often used to describe fibrosis regression that is

adequate to improve clinical outcomes and decrease the risk of decompensation and consequences associated with portal hypertension. Studies that have characterized fibrosis regression following DAAs have only followed patients for 2–3 years, hindering the possibility of tracking long-term histologic changes after SVR[11]. However, most of these studies documented significant fibrosis regression following DAA therapy[12,13]. Tables 1 and 2 show review of different studies assessing fibrosis outcome and hepatic histological changes following DAA therapy[13-37]. Interestingly, fibrosis regression has been proved to continue as far as years following viral eradication; however, fibrosis regression was mainly documented shortly after end of treatment (EOT) partly due to lack of long term follow up. Several recent studies though could manage to follow HCV patients years following viral eradication to clarify this issue[11,18,23].

At the cellular level, variable mechanisms may explain the process of fibrosis regression. Most processes linked to fibrosis regression have been more described than the final destiny of activated HSCs following damage resolution, albeit mostly in animal models. In animal studies, three routes of HSC responses during regression have been identified:

(a) return to a state of inactivity (b) apoptosis/autophagy, (c) cellular senescence. HSCs may return from an active to a quiescent state[38]. The reversion or inactivation of HSCs reflects that the cells move to an inactivated state when liver injury resolves, yet they retain the ability to reawaken faster than fully dormant cells. Such data raise the possibility that reverted HSCs might contribute to the regression of fibrosis, but may promote a rapid progression of fibrosis and a severe recurrence of liver injury[39]. Aging, obesity, diabetes, and other variables have been linked to prolonged liver inflammation and fibrosis after hepatitis C SVR[18]. With the discovery of the Tcf21 transcription factor in mice, as well as additional transcription factors involved in HSC quiescence, such as GATA 4/6, LhX2, RAR, IRF 1/2, PPAR, ETS 1/2, GR, and NF1, the molecular basis for inactivation has recently been studied[40].

Fibrosis regresses, both in experimental and animal models. Eradication of the causative agent of liver fibrosis is the most appropriate way for the resolution of fibrosis by

inducing remodeling of liver vascular architecture and regaining the normal lobular architecture. At some point, liver fibrosis may be reversed by removing the offending cause of liver disase. Regression of liver fibrosis was documented upon early management of cases of autoimmune hepatitis, or hepatitis B virus (HBV) infection[41]. The evolutions of variable inflammatory cascades, activated cells, and fibrogenic cytokines have been postulated as the driving force in liver fibrosis[11]. Similarly, fibrosis regression is associated with myofibroblast deactivation, collagenase enzyme activation, fibrillar cellular matrix disintegration, cell death (senescence and apoptosis of active stellate cells), and fibrous septa resorption[42]. Cirrhosis is a more complicated form of end-stage fibrosis that includes angiogenesis, necro-inflammatory alterations, innate immunity, oxidative stress, tissue hypoxia, and bacterial translocation[43]. The likelihood of fibrosis remission rather than cirrhosis remission is high. However, reversing liver fibrosis does not ensure that the problematic chemical will be removed. The age of an individual, genetic and epigenetic factors, rate of fibrosis progression (slow or rapid fibrosis), and disease-related factors like the etiology and staging of chronic liver disease are all factors that influence the fibrosis regression process. Other possible factors that may cause arrest in fibrosis regression or even cause progression such as liver steatosis with inflammation, alcohol use and diabetes mellitus working as contributing factors for liver injury and fibrosis[18,21]. According to Soliman et.al., 2020; scores of fibrosis regression shows more regression in patients with lower degrees of steatosis and lower body mass index (BMI)[20].

Interference must occur at a certain period for liver fibrosis to be reversible; otherwise, no regression is foreseeable. The "point of no return," or the moment at which the liver is sufficiently damaged that SVR will not reverse the illness, has yet to be defined. It is at this point that liver fibrosis progresses inexorably[20]. It's debatable whether progression and regression rates are connected, indicating that people who advance faster may also regress faster[11]. Despite the lack of evidence, most specialists feel that major regression is unlikely after severe architectural distortion, vascular collapse, and portal hypertension have occurred. This might be due to collagen's substantial

structural cross-linking. As the collagen bands develop, the fibrotic bands are mostly fibrillar collagen. Some of these cross-links are permanent and cannot be destroyed by conventional collagenases, indicating that fibrosis development is unavoidable[44]. As a result, there is limited evidence that extensive areas of parenchymal extinction may be repopulated by regenerated hepatocytes, and vascular lesions in liver cirrhosis often remain with little evidence of full recovery to normal microcirculation in cirrhotic livers[45].

In the IFN era, before deciding for treatment choices, a liver biopsy was the gold standard for appropriate liver fibrosis staging. The majority of studies used paired liver samples to assess fibrosis changes after therapy. Several studies proved that fibrosis regression was documented in patients receiving IFN therapy by liver biopsy and non-invasive liver fibrosis parameters[32,46]. In **the DAA era**, dynamics of fibrosis regression following SVR have not been well identified, particularly because liver biopsy is infrequently performed. The quantity of fibrosis and its physical distribution, other underlying disorders, environmental or hereditary variables, and the variable elements that drive fibrosis advancement may all influence fibrosis regression. There have been no studies to discover genetic factors of fibrosis regression, including single nucleotide polymorphisms, since so few patients have received liver biopsy following HCV SVR due to its limitations[11]. The popularity of non-invasive methods of liver fibrosis staging was related to the advancement of DAA treatments, which had abolished the role of liver biopsy. As a result, most current research looking for fibrosis regression rely on paired or bi-paired non-invasive methods[47,48].

Despite the broad validation of the diagnostic and prognostic value of non-invasive modalities of liver fibrosis assessment, including liver stiffness measurement (LSM) in patients with HCV. Liver stiffness measurement (LSM) is a widely used non-invasive tool for the diagnosis and assessment of degrees of liver fibrosis and has high accuracy[49]. The proper interpretation of LSM in patients after SVR remains unclear. Many studies have shown a substantial reduction in LSM following SVR in HCV patients treated with DAAs[50-52]. It's still unclear if the drop in LSM after HCV

eradication is due to HCV's necro-inflammatory activity being suppressed and changes in hepatic inflammation, rather than the regression of liver fibrosis. However, a large Canadian cohort of HIV-HCV co-infected patients that prospectively evaluated long-term changes in LSM before and after SVR due to DAAs confirmed that LSM after SVR likely indicates a true fibrosis reversal[53].

ANTIVIRAL TREATMENT FOR HCV

Introducing the INF-free DAA has changed the natural history of chronic HCV in the past decade and revolutionized HCV treatment and viral cure. Indeed, improved quality of life is now a reality in most of patients. DAA regimens are safe and highly effective, resulting in sustained virological response rates (SVR) higher than 90%[4]. The last therapeutic regimens approved by Food and Drug Administration and European Medicines Agency are pan-genotypic, once-daily, all-oral DAA combinations that have the potential to close the gaps in the current DAA treatment portfolio. Eight-twelve weeks of treatment is now the standard of care, and viral eradication can be achieved in >95% across different patient populations[54]. As a result, major scientific recommendations have been modified to promote DAA medication for all people who have chronic hepatitis C[4]. Furthermore, a recent large cohort research found that DAA therapy is linked to a lower risk of death and hepatocellular carcinoma (HCC), confirming SVR's long-term impact[55]. However, the risk of liver-related events persists in patients with HCV who have cleared the virus, particularly in those who had advanced fibrosis and cirrhosis prior to treatment[11].

EVALUATION OF FIBROSIS

In the INF era, liver biopsy was the most accurate approach for making treatment choices as a precise assessment of liver fibrosis[56]. Therefore, the variable protocols of DAA therapies for HCV treatment had adopted reliance on non-invasive modalities of assessment of liver fibrosis. However, the existing non-invasive clinical and laboratory scores for assessing liver fibrosis performed poorly and inaccurately, failing to separate

the phases of liver fibrosis' dynamic progression. Additionally, sophisticated imaging methods such as transient elastography (TE), shear wave (SW), acoustic radiation force impulse elastography (ARFI), and magnetic resonance elastography are available to quantify liver stiffness (LS) utilising a fibroscan instrument (MRE)[57]. However, it is important to interpret LSM cautiously as many studies denoted that liver stiffness could be affected by the presence of hepatic steatosis; and that the presence of severe steatosis, detected by histology or by US, should always be taken into account in order to avoid overestimations of liver stiffness[58,59]. In fact, higher LSM values in the presence of liver steatosis have been reported in patients with chronic HCV[60]. It was also reported that high body mass index BMI values negatively affected the diagnostic reliability[61]. Other limitations include the presence of tissue abnormalities, such as edema or inflammation which can interfere with LSM, independently of fibrosis stressing that LSM should be cautiously interpreted in such cases[62].

Finally, there is no perfect single test solution, as serological markers are good at assessing the advanced fibrosis stages only, making them inaccurate in mild to moderate fibrosis cases. So, it was suggested to use two non-invasive methods for assessing liver fibrosis, one imaging and the other serum marker, to be more effective and reliable[2]. Despite the high costs, time-consuming matter, and refusal of some patients, MRI elastography is a promising and more accurate tool for assessing liver fibrosis[47].

A widely accessible, reliable, accurate, reproducible, simple, and dynamic assessment of liver fibrosis development and reversal is still needed. In hepatology research, this seems to be an unmet need. Because the quantity of deposited collagens in each stage are not multiples of the preceding stage, the difference between liver fibrosis stages is a qualitative rather than a quantitative linear measure[63]. Late stages of fibrosis need more collagenases than early stages. Similarly, the non-uniform deposition of collagen in connection to time intervals is obvious, and variations in LS measurement in later stages may be within the same stage of fibrosis for the large number of people included[64].

HISTOPATHOLOGICAL FEATURES OF FIBROSIS REGRESSION

There is no agreement on the suggested histological staging system for chronic viral hepatitis after therapy. Histological examination is best done on paired liver samples, one taken before treatment begins and the other taken at least six months after the end of treatment (EOT). Fibrosis regression was formerly defined as a drop of at least one point in either the METAVIR or the histological activity index score from baseline to post-treatment assessment. The four-stage METAVIR fibrosis grading system was used to determine the fibrosis stage[37]. Stage 4 cirrhosis is further split into three categories based on fibrous septa thickness and nodule size, which correctly associated with clinical stage and the probability of hepatocellular carcinoma recurrence following curative resection[65]. Another scoring method is the hepatic repair complex, which is based on important histology features that indicate cirrhosis regression. The delicate perforated septa, isolated thick collagen fibres, thin peri-portal fibrous spikes, hepatic vein remnants with prolapsed hepatocytes, split septa interrupted by clusters or cords of hepatocytes, and aberrant parenchymal vein are all histological observations that support this system[66]. The Beijing classification, P-I-R Score, is a novel tool for dynamic assessment of fibrosis advancement versus regression (predominantly regressive, indeterminate, and predominantly progressive). This system was proposed by Sun *et al* (2017) to evaluate chronic HBV before and after treatment[66,67].

More rigorous efforts are still required to respect the heterogeneous nature of the cirrhosis process to incorporate regression features and formulate a valid scoring system for better evaluation of fibrosis and activity regression in chronic liver diseases. In the assessment of fibrosis regression after HCV therapy, however, the improvement of digital pathology and the introduction of morphometry in determining collagen proportional area was noteworthy. Furthermore, second-harmonic generation/two-photon excitation fluorescence (SHG/TPEF), a quantitative measure of liver fibrosis width, is thought to be the most accurate predictor of fibrosis regression[33].

Multiple studies addressed fibrosis regression following HCV treatment with INF and DAAs using invasive and non-invasive tools as shown in table 1 and 2. Conversely, reversal of liver inflammation and fibrosis was achieved in a significant number of patients treated with DAAs using histological assessment by liver biopsy[13-37].

HEPATOCELLULAR CARCINOMA (HCC) POST-DAAS AND RELATION TO FIBROSIS REGRESSION

A 76% reduction in the risk of developing HCC in patients achieving SVR following IFN therapy has been documented by a meta-analysis[68]. However, some studies have pointed out that DAAs could instead augment the development of HCC. Despite the conflicting data regarding this issue in many studies, it was settled that HCV eradication has a protective effect against HCC development, regardless antiviral therapy. Response to treatment (SVR or non-SVR) was the sole independent predictor of HCC recurrence following curative treatment, rather than the type of antiviral treatment (IFN or DAA)[69].

Following the achievement of SVR, fibrosis regression reached its plateau for about one year. In addition, the fibrosis regression does not prevent the development of HCC years after treatment as liver, although deprived of the pro-inflammatory viral trigger, still has a potentially carcinogenic persistence[70,71]. Therefore, because of the insufficient data regarding the decrease in HCC risk after SVR with DAAs, patients, especially those with severe fibrosis, should be committed to frequent HCC screening.

EFFECT OF FIBROSIS REGRESSION ON CLINICAL OUTCOMES

There is strong accumulating evidence that HCV eradication in all patients, besides patients with baseline cirrhosis, leads to improved clinical outcomes. A wide range of effects of HCV elimination exist. These include an overall reduction in mortality and the risk of HCC in patients with advanced fibrosis, and a reduction in extrahepatic manifestations, *e.g.* HCV-related non-Hodgkin's lymphoma, other lymphoproliferative disorders, and cryoglobulinemic vasculitis[72,73]. Additionally, DAA-induced HCV

clearance has been shown to decrease the risk of cardiovascular events in addition to the incidence of type 2 DM incidence probably by restoring the disordered glucose homeostasis[74,75]. Improvement in fibrosis, which seems to be a main driver of cirrhosis sequelae, will almost certainly lead to clinical improvement, even in patients with portal hypertension[11]. The long-term effects of fibrosis regression, however, are yet unknown. Furthermore, it has to be determined if the improved clinical outcome is due to successful causative therapy or fibrosis regression. Wu et al. (2017) looked at patients with compensated cirrhosis precipitated by HBV and found that changes in LS throughout the first 26 weeks might predict decompensations and HCC with antiviral therapy[76]. This might indicate that fibrosis regression has clinical implications. Cirrhosis regression was linked to lower morbidity and increased mortality in another HCV retrospective study[77]. However, there is currently a dearth of direct and convincing evidence that biopsy-proven fibrosis regression improves clinical outcomes. The more serious the underlying liver disease (particularly in individuals with advanced fibrosis and portal hypertension), the less likely the patient is to evade problems. Some individuals with severe liver disease and sequelae, on the other hand, may improve[11].

CONCLUSION

Despite the amazing progress in HCV treatment using DAAs, information about its role in fibrosis regression is still inadequate. If the non-invasive methods for assessing liver fibrosis are suitable for assessing regression, it needs much research. Regression of liver fibrosis in cirrhotic patients and those with advanced fibrosis will remain a hope that both physicians and patients seek.

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