THE EVOLUTION OF LIVER FIBROSIS IN PATIENTS WITH VIRAL C INFECTION POST ORAL ANTIVIRAL TREATMENT

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Abstract

Hepatitis C virus infection has been for several decades the major cause of cirrhosis and its complications worldwide. However, an arsenal of new and highly effective oral direct-acting antiviral drugs has changed the course of HCV treatment. The effects of HCV elimination are broad and include an overall reduction in mortality in patients with advanced fibrosis, a reduction of the risk of HCC in patients with advanced fibrosis and a reduction in extrahepatic manifestations including HCV-related non-Hodgkin's lymphoma, other lymphoproliferative disorders and cryoglobulinemic vasculitis. Fibrosis regression is associated with a broad clinical benefit and remains an important therapeutic target in HCV patients who have obtained RSV.

Keywords: *hepatitis C virus, fibrosis, cirrhosis, oral direct-acting antiviral drugs.*

Rezumat

Infecția cu virusul hepatitic C reprezintă, de câteva decenii, cauza majoră a cirozei și a complicațiilor acesteia la nivel mondial. Cu toate acestea, arsenalul de medicamente antivirale orale cu acțiune directă, noi și foarte eficiente, a schimbat cursul tratamentului hepatitei virale C. Efectele eliminării virusului hepatitic C sunt ample și includ o reducere generală a mortalității la pacienții cu fibroză avansată, reducerea riscului de hepatocarcinom la pacienții cu fibroză avansată și reducerea manifestărilor extrahepatice, inclusiv limfomul non-Hodgkin, alte tulburări limfoproliferative și vasculită crioglobulinemică. Regresia fibrozei este asociată cu un beneficiu clinic larg și rămâne o țintă terapeutică importantă la pacienții cu hepatită virală C care au obținut răspuns viral susținut.

Cuvinte cheie: *virus hepatitic C, fibroză, ciroză, medicamente antivirale orale cu acțiune directă.*



Internal Medicine

General Reviews

Introduction

Hepatitis C virus (HCV) infection has been for several decades the major cause of cirrhosis and its complications worldwide. Treatment for HCV infection with interferon (IFN) was associated with moderate success and showed frequent adverse effects. More recently, however, an arsenal of new and highly effective oral direct-acting antiviral drugs (DAA) has changed the course of HCV treatment in a wide range of patients, including those with advanced fibrosis, compensated and decompensated cirrhosis, regardless of other comorbidities.

Fibrosis regression

Liver fibrosis is characterized as a reversible wound-healing process, which is mainly triggered by chronic liver tissue injury. Actually, liver fibrosis is a beneficial process at the beginning, because this process helps liver to repair its incomplete tissues and to restore its complete mass after the liver suffers from different kinds of acute injuries. However, if the injury is continuous and longstanding, liver fibrosis will unavoidably result in liver cirrhosis[1].

Fibrosis can regress, both in experimental models[2] and in human liver disease[3]. Although the progression of fibrosis is often described as linear along a continuum 0-4 stage (in typical staging systems), this statement is simplified. In fact, the progression of fibrosis tends to accelerate as the disease progresses, especially towards more advanced stages[4]. The rate of fibrosis progression in viral hepatopathy C has been associated with a number of factors, including body mass index, alcoholic or nonalcoholic fatty liver disease, human immunodeficiency virus (HIV) infection, and genetic factors[5].

The dynamics of fibrosis regression after sustained virologic response (SVR) has not been well defined, largely because liver biopsy is rarely performed after SVR.

Remarkably, the definition of fibrosis regression has not been standardised, but generally indicates a reduction in fibrosis content.

This functional definition does not, however, take into account other changes in liver architecture - especially in the cirrhotic liver - for example, changes in nodule size, the extent of terminal venule collapse, regeneration elements or altered distributions of collagen and other extracellular matrix components. Moreover, the few studies that characterized the regression of fibrosis (especially after DAA therapy) followed patients for only 2-3 years, making it impossible to follow long-term histological changes after SVR. It is likely, but not established, that the regression of fibrosis also

varies between different types of lesions. For example, biliary fibrosis is easily reversible in animal models and can lead to the complete removal of excessive collagen[6]. A study which included 130 SVR patients (from 2003 to 2020) shows that downregulated liver angiogenesis significantly explains the collagen proportionate area regression[7].

An unknown element in fibrosis regression is the "point of no return". In other words, when is the liver so sick that there will be no regression after SVR? Although there are few data, most experts believe that once there are severe architectural distortions, vascular collapse and portal hypertension, significant regression is less likely[8].

Clinical considerations in fibrosis regression

Although there is no standardized definition of "clinically significant regression of fibrosis", we propose that the term is best used to indicate fibrosis regression enough to improve clinical outcomes either by reducing the risk of decompensation with complications of portal hypertension (development of ascites and varicose veins) or encephalopathy, or by reducing the risk of hepatocellular carcinoma (HCC).

Although HCV clearance is associated with fibrosis reversal / regression in many patients, it has not been established what histological or clinical features predict who will regress after SVR.

Two studies indicate that patients with low levels of HCV RNA pre-treatment may be more likely to have a regression of liver fibrosis after interferon-based therapy. Interestingly, after SVR, a small proportion of patients (12% in one study) may have progressive liver disease. Although in most cases this is probably due to other comorbid causes of liver disease (alcoholism or NASH - Non-alcoholic steatohepatitis), the progression may be unexplicable in some patients[9].

In a study evaluating untreated HCV patients, the median increase in collagen was 27% over 52 weeks, associated with a mean increase in smooth muscle alpha actin (a marker of hepatic stellate cells activation) of 49%, indicating the active progression of fibrosis. In the HALT-C study, which assessed the effect of maintenance therapy with peginterferon-ribavirin, the main group of 346 unresponsive individuals had a mean increase in fibrosis of 61% after 2 years compared to the pretreatment baseline and 80% after 4 years[10].

Notably, these studies included patients with a wide range of liver fibrosis degree; it is unclear whether patients with advanced fibrosis and cirrhosis have the same progress rate as patients with less significant fibrosis. However, even in subjects with histological cirrhosis, fibrosis continues to progress.

In chronic HCV infection, therapy-induced SVR is a clinically meaningful end point. SVR is a durable marker of viral eradication, because evidence for extrahepatic residual viremia is limited, and multiple reports demonstrate that late relapse is rarely observed; SVR is tantamount to cure[11].

Usually, one-third to two-thirds of patients with HCV eradication will present fibrosis regression, although subjects with cirrhosis have lower rates of regression than those with mild-moderate fibrosis. However, there are some aspects which need to be mentioned; first, many early studies of regression assessment have been performed in patients treated with IFN-based therapy and it is not known whether fibrosis regression is similar between the two types of HCV treatment. Second, data from the DAA



Internal Medicine

General Reviews

era are limited by the short duration of follow-up after HCV elimination. Third, although early studies used histological assessment to measure regression of fibrosis, more recent studies have characterized the response to therapy using noninvasive methods[12]. Although noninvasive assessments may not be as accurate as histological assessment, trends toward fibrosis reversal are clear.

However, it is essential to recognize that many noninvasive approaches currently used are driven by the inflammatory response (both for blood markers and liver stiffness) and may therefore lead to the conclusion that fibrosis regression is more pronounced because the inflammatory response was subdued.

A long-term follow-up study of 415 HCV patients with advanced fibrosis performed repeated non-invasive fibrosis assessments (FibroTest and transient elastography). 108 patients obtained SVR with IFN-based therapy and 49% of them had a reduction >20% of FibroTest scores, which was higher than in 219 subjects who did not respond to treatment (23%; P <0.001 vs SVR). In patients with cirrhosis, regression occurred in 24/43 patients, but 15% of the other patients with SVR progressed to hepatic cirrhosis[13]. Another large long-term study included 4731 patients with HCV infection, of whom 1657 were treated and 755 had SVR; over a 10-year period, there was an overall 22% reduction in fibrosis in patients with SVR[14].

In addition, SVR has been associated with long-term maintenance of fibrosis regression. Reversal of fibrosis has also been studied in several special groups, including those with recurrent HCV after transplantation and HIV-HCV co-infected patients. In a post-transplant HCV study (mostly patients with mild fibrosis), eradication of HCV with IFN-based therapy resulted in a dramatic reduction in fibrosis progression compared to those who did not respond or relapsed[15]. In addition, in the SVR group, 13% progressed to fibrosis stage 3 on post-treatment biopsies vs 38% in the unanswered / relapse group (P =0.001). Another study performed on 77 patients after liver transplantation found that SVR after DAA treatment led to a significant regression of fibrosis.

Finally, in 112 patients with recurrent HCV who were treated after liver transplantation, there was a significant regression of fibrosis at all stages of fibrosis[16] and 43% of patients had a regression of at least one stage of liver fibrosis. In addition, in the 34 patients who met the definition of cirrhosis, liver stiffness decreased from 25.3 (16.5-32.8) to 14.5 (9.9-22.1) kPa.

Clinical staging of fibrosis has been an obstacle to the accurate assessment of fibrosis regression after SVR. Liver histology is considered the golden standard for staging fibrosis, but liver biopsy is invasive and not routinely performed. A variety of methods

range from the use of physical findings to routine laboratory tests, such as platelets, blood-based testing algorithms that use commonly available blood tests, or even serum markers of fibrosis have been widely studied in HCV patients. AST to Platelet Ratio Index (APRI) or Fibrosis-*4 (*FIB-4) are also useful and easy to use.

However, blood tests usually have a high sensitivity and specificity for the detection of advanced fibrosis and cirrhosis, but are not very sensitive or specific for initial stages of fibrosis[17].

Imaging, especially transient elastography for vibration control, also called transient elastography (TE) and magnetic resonance elastography (MRE), which measure liver stiffness, are appealing for staging fibrosis because they are noninvasive. TE has been extensively studied in HCV and is very specific when liver stiffness is extreme (low, excludes advanced fibrosis; high, consistent with advanced fibrosis.) However, it is inaccurate regarding intermediate levels of stiffness[18].

MRE is more sensitive because it is noninvasive and includes a large area of the liver, which may reduce sampling variability reflecting heterogeneity in fibrosis distribution. Few studies have compared TE and MRE in patients with HCV cirrhosis, and after SVR MRE leads to more false-positive diagnoses of cirrhosis than TE in HCV patients.

TE may also be limited by high failure rates in patients with narrow intercostal spaces and citation or interference with extrahepatic cholestasis, liver inflammation and steatosis. TE probably overestimates the regression of fibrosis after HCV elimination due to the rapid decrease in inflammation typical of DAA therapy, as inflammation increases stiffness as well.

Effects of HCV elimination and fibrosis regression on clinical outcomes

Evidence that HCV eradication in all patients, and specifically in patients with initial cirrhosis, leads to improved clinical outcomes, not only after IFN-based therapy but also for DAA, is constantly mentioned[19]. The effects of HCV elimination are broad and include an overall reduction in mortality in patients with advanced fibrosis, a reduction of the risk of HCC in patients with advanced fibrosis and a reduction in extrahepatic manifestations including HCV-related non-Hodgkin's lymphoma, other lymphoproliferative disorders and cryoglobulinemic vasculitis[20].

DAA-mediated HCV elimination in patients with cirrhosis leads to consistent improvements regarding complication rates and clinical outcomes[21].

In a DAA study on cirrhosis patients in the United Kingdom, those treated with DAA had a mean reduction in the MELD score of 0.85, while untreated patients had an average increase in the MELD score of 0.75. This is remarkable because the patients included in this study had an extremely advanced disease. In one study[22], which compared 2 cohorts with HCV cirrhosis (one DAA cohort [n =196] and one control cohort that did not receive HCV therapy in a similar time frame [n =182]), incidence of liver-related hospitalizations, HCC, liver transplantation and death were measured (follow-up was 18 and 20 months, respectively). The SVR for the treated group was 87% and 89% respectively (122/137) in Child-Pugh A, and 81% (48/59) in Child-Pugh B/C. The hospitalization rate was 29.1 hospitalizations per 100 person-years in the control group, compared to 10.4 in the DAA group. However, there was no difference in the incidence of hospitalizations in patients with Child-Pugh C and in the short follow-up period



there were no differences in the incidence of HCC, liver transplantation or death between cohorts. In patients with compensated cirrhosis, the improvement in fibrosis is likely to lead to clinical improvement, including subjects with portal hypertension. The more severe the underlying liver disease (especially in those with advanced fibrosis and portal hypertension), the less likely the patient is to avoid future complications.

The clinical outcomes of some patients with decompen-sated cirrhosis could be improved after the suppression of etiological factors and by targeting the key factors of pathogenesis. Those patients may become "recompen-sated," which means that decompensated complications may not occur in these patients a long period, particularly in patients with alcoholic and viral-related decompensations. However, the definition and stability of "re-compensation" are still unclear[23].

Monitoring the development of HCC after HCV elimination

The optimal management of SVR patients is not yet clarified. This is especially true in patients who have had advanced fibrosis at the beginning of antiviral therapy, including those with compensated cirrhosis. Molecular analysis of liver tissue can identify high-risk genetic signatures that predict a higher risk of HCC. The hepatic venous pressure gradient (HVPG) could be useful in identifying those with clinically significant portal hypertension. However, HVPG is invasive and not easy to perform in most patients, although it may be useful in cirrhosis. Regardless, the risk of HCC is increased in patients with fibrosis at the time of SVR, and therefore HCC screening should be continued indefinitely after SVR until more data are available.

Summary and future perspectives

Fibrosis regression is associated with a broad clinical benefit and remains an important therapeutic target in HCV patients who have obtained RSV and have a degree of advanced liver fibrosis that does not improve spontaneously after virological elimination.

Substantial gaps remain in both the biology of fibrosis regression and its clinical features. From a mechanical perspective, there must be much more precision regarding the regulation of liver fibrosis regression. As mentioned, it is not known what type of cellular and molecular events allow the regeneration of a healthy liver without fibrosis, or blocking regeneration when there are advanced stages of fibrosis.

The remaining gaps include determining which patients can expect significant reversal of fibrosis after HCV elimination, what factors influence fibrosis regression (including whether regression can be anticipated based on clinical parameters), and whether there are genetic determinants of fibrosis regression, as there are for the progression of

fibrosis. Furthermore, how can we assess the regression of liver fibrosis without relying on liver biopsy and what implications will the noninvasive evidence of regression have on patient management and HCC screening? And most important of all, can we use this information to optimize the diagnosis and treatment of fibrotic liver disease to induce regression of existing scarring to improve outcomes and reduce the risk of HCC? With these questions still unanswered, cirrhosis management in post-SVR patients is likely to evolve, and the ongoing study of these patients will lead to progress that should significantly improve advanced liver fibrosis.

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