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Evaluation of HCV-related liver fibrosis post-successful DAA therapy

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Abstract

Background: The rapidly developing era of direct-acting antiviral regimens (DAAs) for more than one hepatitis C virus (HCV) genotype had certainly alleviated HCV burden all over the world. Liver fibrosis is the major dramatic complication of HCV infection, and its progression leads to cirrhosis, liver failure, and hepatocellular carcinoma. The impact of DAAs on liver fibrosis had been debatably evaluated with undetermined resolution.

Main body: The aim of this review is to accurately revise the effects of DAA regimens on liver fibrosis which can either be regression, progression, or non-significant association. Liver fibrosis regression is a genuine fact assured by many retrospective and prospective clinical studies. Evaluation could be concluded early post-therapy reflecting the dynamic nature of the process.

Conclusions: The ideal application of DAA regimens in treating HCV has to be accomplished with efficient non-invasive markers in differentiating proper fibrosis evaluation from necroinflammation consequences. Liver biopsy is the gold standard that visualizes the dynamic of fibrosis regression.

Keywords: Direct-acting antivirals, Hepatitis C virus, Liver fibrosis, Sustained viral response

Background

The advent of DAA therapies against HCV infection is considered by many as the most momentous scientific event taking place in the last few years [1]. Before the developing era of DAAs, HCV infection represented more than 70% of chronic liver disease morbidity and mortality especially in countries with high HCV burden [2]. Nowadays, the outstanding results of DAA therapies had tardily listed HCV in newly reported etiologies of liver diseases [1]. However, the encumbrance of HCV-related liver fibrosis progressing to cirrhosis, hepatocellular carcinoma, and decompensated liver disease is still ensuing [3]. The foreseeable end of these HCV-related disorders is linked to the death of the last untreatable case, which is expected to be by 2030 [2]. Nevertheless, the most important question is: are these therapies capable of regressing fibrosis or even stopping the progression of this definite dynamic process?

Main text

Does fibrosis really regress?

Remodeling of liver vascular and regaining the normal lobular architecture upon removal of the incriminating factor is the ultimate hope of liver researchers. As a rule, removing the offender is the most accurate way of reaching a resolution [4]. Accordingly, liver fibrosis—at a certain point—is capable of regression by directly eliminating the cause. Reportedly, on well-targeted early treated autoimmune hepatitis, or hepatitis B virus (HBV) infection, regression of fibrosis was a possible prospective [4].

Liver fibrosis is crucially linked to the evolution of certain inflammatory cascades, activated cells, and fibrogenic cytokines [5]. Likewise, in fibrosis regression, the convoluted process of fibrosis regression is reported to be simultaneous with deactivated myofibroblasts, mounting of collagenases enzymes, fibrillar cellular

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matrix degradation, ending with cell death (senescence and apoptosis of activated stellate cells), and resorption of fibrous septa [6]. Concerning cirrhosis, a more complex end-stage fibrosis, it comprises angiogenesis, necroinflammation, innate immunity, oxidative stress, tissue hypoxia, and bacterial translocation [7]. Accordingly, regression of fibrosis rather than cirrhosis is considered as a likely prospective. Nevertheless, liver fibrosis regression is not guaranteed to take place on treating the offending agent. Many factors had been demarcated to be of influence on the occurrence of fibrosis regression process: individual's age, genetic and epigenetic factors, and rate of fibrosis progression (slow or rapid fibrosis), or disease-related factors like etiology and staging of chronic liver disease [8–12].

For liver fibrosis to be evitable, interference should be at a certain time; otherwise, no regression is predictable. The point of no return is that at which liver fibrosis progression is inevitable [13]. The cause might be structural extensive crosslinks developed in collagen, the fibrotic bands consisting mainly of fibrillar collagen, as the collagen bands mature. Some of these crosslinks are irreversible and cannot be degraded by the normal collagenases representing a point of unavoidable fibrosis progression [13].

Evaluation of fibrosis

In the era of interferon (IFN), liver biopsy was the most accountable determinant of treatment decision as a precise measure of liver fibrosis [14].

The contemporary protocols of DAA HCV therapies had adopted reliance on non-invasiveness [15, 16]. The currently handled non-invasive hybrid clinical and laboratory scores of liver fibrosis had performed poorly inaccurate, with failure to distinguish the stages of the dynamic evolutions of liver fibrosis. Moreover, the performance of the more advanced imaging measures that assess liver stiffness (LS) with a fibroscan device like transient elastography (TE), shear wave (SW), acoustic radiation force impulse elastography (ARFI), and magnetic resonance elastography (MRE) [15, 16]. Eventually, there is no perfect one test solution, as serum markers are good at the ends but too soft in the middle. It was found that to be more effective, several tests have to be used together, such as 2 biomarker tests or one biomarker and an elastography test [17].. Despite the high costs, tuning to MRI elastography is said to be promising [18].

The substantial necessity of a widely available accurate, reproductive, and dynamic measure of liver fibrosis progression, and likewise regression, is still representing an unmet need in hepatology research.

It is noteworthy to mention that the difference between liver fibrosis stages is a qualitative rather than a quantitative linear measure, as the amounts of deposited collagens in each stage are not the multiple of the previous stage [19]. Accordingly, more collagenases are needed in late fibrosis stages than earlier ones [9]. Similarly, the non-linearity of collagen deposition in relation to the time interval is evidently clear. Notably, the changes in LS measurement in advanced stages might be within the same stage of fibrosis for the wide included range of numbers [20].

Histopathological features of fibrosis regression

There was no consensus for the proposed histological scoring system for chronic viral hepatitis post-treatment. Histological evaluations are better performed on paired liver biopsies: one obtained before initiation of the therapy and the other at least 6 months after the end of treatment (EOT). In the previous studies, regression was defined as a decrease of at least one point in either METAVIR or histology activity index (HAI) score from baseline to post-treatment evaluation [21, 22].

Fibrosis stage was assessed using the four stages METAVIR fibrosis scoring system [23]. Subsequently, stage 4 cirrhosis was further subdivided into three subgroups based on the thickness of fibrous septa and the size of the nodules that properly correlated with the clinical stage as well as the risk of hepatocellular carcinoma recurrence after curative resection. Stage 4A is characterized by mild cirrhosis with thin septa (definite or probable), stage 4B is moderate cirrhosis showing at occasional broad fibrous septa, and stage 4C refers to severe cirrhosis in which at least one very broad septum or many micronodules are present [24, 25]. The grade of necro-inflammatory activity was assessed using the HAI criteria with a maximum score of HAI is 18 [26].

Hepatic repair complex is another scoring system that depends on the presence of relevant histological findings that implies a regression of cirrhosis. This system relied on the histological findings of perforated delicate septa, isolated thick collagen fibers, thin periportal fibrous spikes, hepatic vein remnants with prolapsed hepatocytes, split septa interrupted by clusters or cords of hepatocytes, and aberrant parenchymal veins [27].

The Beijing classification, P-I-R Score (predominantly regressive, indeterminate, and predominantly progressive), is a unique method that provides a dynamic evaluation of the fibrosis course progression versus regression. This system was proposed by Sun et al., in the evaluation of chronic HBV pre- and post-therapy [28]. Fibrosis was assessed using routine hematoxylin and eosin, reticulin, and trichrome stains. The cases were sub-classified into predominantly progressive fibrosis in which most fibrous septa were broad, with loosely aggregated pale stained collagen infiltrated by inflammatory cells and ductular reactions; indeterminate fibrosis

midway between progressive and regressive fibrosis; and predominantly regressive in which most fibrous septa showed thin, dense, and acellular stroma lack capillary vascular proliferation and staining deeply on trichrome stain.

Since liver cirrhosis is a heterogeneous process, future efforts are recommended to incorporate features of regression and validate a staging system for better assessment of fibrosis and necro-inflammation regression in chronic liver diseases [29].

Advancement of the digital pathology and the application of morphometry in the assessment of collagen proportionate area (CPA) was impressive in the detection of fibrosis regression post-HCV treatment [30]. In addition, second harmonic generation/two-photon excitation fluorescence (SHG/TPEF), a quantitative assessment of liver fibrosis width, assumed to be the most predictive feature indicative of fibrosis regression [31, 32].

Fibrosis regression in recovered HCV patients

Fibrosis regression evaluation post-treating HCV should be done only after at least 1 year of achieving sustained virological response (SVR). Earlier performed studies should not be significantly considered for their inaccurate conclusions.

In the IFN era

Liver biopsy was the gold standard relied on for proper pretreatment staging of liver fibrosis and treatment decisions. Most studies performed for post-treatment evaluation of fibrosis were dependent on paired liver biopsies [14].

The remarkable, pooled study of Poynard et al. tested the effect of different types of IFN containing regimens on liver fibrosis and even cirrhosis. The study enrolled 4493 patients from four randomized trials of pegylated (PEG) IFN alfa-2b (IFN α2b) alone, in combination with ribavirin (RBV), or of combined IFN α2b and (RBV) [33–36]. At the initial biopsy, 75% had no significant fibrosis while 25% had significant fibrosis with the mean METAVIR fibrosis stage ranging from 1.3 to 1.5. The SVR rate varied significantly from 5 to 63% according to the regimen. In patients with SVR, there was less fibrosis progression (7% versus 17% and 21% in relapsers and non-responders, respectively). However, independent of achieving an SVR, young patients (< 40 years old) with low body mass index (less than 27) and who had a low fibrosis stage at baseline are at low risk of fibrosis progression. A paired biopsy was available from 3010 patients with a 20-month mean duration between the biopsies. The histological response showed improvement in the fibrosis stage in 55% of patients, no change in 31%, and an upstage in 14% of the cases. In addition, fibrosis progression was the worst in patients treated with IFN for 24 weeks. The second biopsy stated that cirrhosis was observed in 6% versus 10% of patients treated with reinforced regimens compared to non-treated patients. Even more, nearly half of the treated patients showed a reversal of cirrhosis; however, the difference was a one-stage change [37]. Another study enrolled 150 patients who achieved SVR after a combinational treatment therapy of IFN α2b and RBV. Pre-treatment liver biopsies highlighted the stage of fibrosis to be stage 2 and 6 in 77% and 11%, respectively. A 5-year follow-up documented a noteworthy fibrosis regression in about 81.5%. Of the 12 patients with advanced fibrosis/cirrhosis, ten had decreased fibrosis scores in a range of two points or greater [38]. However, a large long-term (10 years) observational study assessing the regression of fibrosis on IFN-treated HCV patients relying on non-invasive liver fibrosis parameters (APRI score and FIB4 formula) had also addressed remarkable regression proven in those with SVR achievement [39].

In DAA era

The advent of DAA therapies was associated with the prevalence of the non-invasive measures of liver fibrosis staging and had eliminated the role of liver biopsy [40]. Accordingly, most studies searching for fibrosis regression are currently dependable on paired or bi-paired non-invasive measures [15–19]. In a study carried by Knop et al. on 54 cirrhotic patients revealed a reduction of LS in 88% and 57% of DAA-treated patients after 6 months of achieving SVR using TE and AFRI techniques, respectively [41]. Based on the non-invasive scores, liver transplant recipients were also evaluated for fibrosis reversal on a 3-month interval of DAA therapy of HCV [42]. Martini et al. monitored 125 post-transplanted patients treated with DAAs using TE and found a stepwise decline of LS from 20.4 to 17.5 to 14.0 kPa at 6 and 12 months, respectively [43]. Another study on 112 patients received IFN/DAAs post-transplantation and followed up for 1 year demonstrated that a nearly 43.2% and 72–85% of cirrhotic and remaining stages patients showed histological evidence of fibrosis regression at least 1-metavir stage, respectively [44]. A 6-month interval study performed on 51 post-transplant patients followed up for 1 year after achieving SVR using SW, TE, and ARFI showed at least a 20% decrease in LS compared with baseline [45]. Despite the short-term follow-up, Elraziky et al. in their study which was dependent on TE, PRI, and FIB 4 in the assessment of fibrosis revealed fibrosis regression in 27.5% of patients 3 months after SVR. Treated cirrhotic patients experienced fibrosis regression irrespective of their therapy regimens, whereas fibrosis regression was dependent on achieving SVR in cirrhotic patients [46]. A similar prospective study adopting SW was performed serially for 6

months post-treatment pledging the assumption of early regression post-DAA therapies [47]. An 18-month study had evaluated the changes in LS through TE, APRI, and FIB4 scores following DAA therapies, revealing a significant alleviation of liver stiffness among SVR achievers [48]. ARFI was the nominated measure of LS in the study of Chen et al., who reported a significant decrease in fibrosis measures on 24 weeks post-treatment follow-up [49]. Nearly 25.5% of cirrhotic patients followed up for 1 year declined to 18.1% on TE [50]. Prakash et al. demonstrated that 39% of cirrhotic patients declined to < 2.67 on FIB 4 monitoring technique [51]. The most promising MRE had been adopted for a short-term study of assessing fibrosis regression coinciding with SVR detecting. Surprisingly, a significant reduction in the fibrosis burden was evidenced by an acute lessening in liver T1, T2, and T2* and a liver perfusion upsurge [18].

Soliman et al. had assessed the degree of fibrosis regression through TE, in a 1-year interval, and had substantially confined the role of DAAs in regression of fibrosis either with or without IFNs [12]. Another 1-year comparative retrospective Egyptian study had delineated a higher rate of regression of fibrosis in DAAs successfully treated cases (52.5%) than those who were responsive to IFN treatment (23.3%). In this study, reliance was based on TE for the DAA-treated group versus liver biopsy in the IFN group [52].

However, all these studies have raised a significant concern about the credibility of all used parameters in genuine assessment of fibrosis regression, or these are the penalties of alleviated necroinflammation following the direct viral effects of these drugs. So, despite the marvelous achievement of the therapeutic goal of DAAs, more meticulous judging measures are still needed for better appraisal of the proposed residual liver disease burden following the end of therapy. Assumptions had to be delineated for planning better strategies directed to HCV-related liver disease burden complete elimination.

Hepatocellular carcinoma (HCC) post-DAA versus IFN regimens

A meta-analysis of twelve studies showed a reduction in HCC risk of 76% in patients achieving SVR following IFN therapy [53]. On the other hand, conflicting data appeared regarding the risk of HCC occurrence and recurrence post-DAAs treatment. Three studies reported that DAA-induced SVR did not reduce the occurrence and recurrence of HCC; however, these studies were small-size, single-centered of short-term follow-up cohorts [54–56]. The possible explanation is that a rapid HCV suppression mediated immunological changes and induced a more aggressive HCC. Furthermore, HBV reactivation in the setting of DAA use has been reported which may co-operate in HCC development [57]. The follow-up of 344 cirrhotic patients without HCC treated with DAAs for 6 months revealed the occurrence of HCC in 9/285 patients (3.2%) and recurrence in 17/59 patients (28.8%). Conti et al. assumed the high HCC risk was related to the Child-Pugh class and prior HCC history rather than HCV genotype or DAA regimen [55]. Other reports suggested the risk of HCC was 9% within 6 months and 7.4% within 12 months follow-up [54, 56]. In contrast, large cohort studies have demonstrated a reduced risk of HCC in patients achieving SVR post-DAA regimen [58–60]. The risk of HCC was 1.2% among 22,500 patients treated with DAAs of which 0.8% had achieved SVR. The main co-factors for the development of HCC in that study were liver cirrhosis and failure of achieving SVR [58]. In a retrospective study including more than 60,000 HCV patients treated with antiviral therapy either DAAs, IFN-based regimens, or combined regimens, achievement of SVR was the main factor associated with low HCC risk regardless of the antiviral regimen [60]. A systematic meta-analysis of 26 observational studies on HCC occurrence following different anti-viral therapies (IFN = 17, DAAs = 9 studies) reported higher HCC risk in DAA-treated patients compared to IFN. However, the higher risk was alleviated after adjustment for study follow-up and age. DAA-treated patients were older and had a short follow-up duration [61]. Additionally, in a large cohort of 17,836 HCV-infected either treated with IFN or DAAs revealed a significantly higher HCC incidence rate than IFN treated patients. DAA-treated patients were of older age with elevated serum AFP and had liver cirrhosis, the main risk factors for HCC occurrence. A sub-analysis in cirrhotic patients showed a high risk of HCC in untreated patients with an equal risk in both treated patients [59]. Mariño et al. reported a 3.73% risk of developing HCC in 1123 cirrhotic patients treated with DAAs; the risk was higher in patients without SVR, who had more severe diseases (Child B or C, decompensation or high liver stiffness) and atypical nodules [62].

The risk of HCC recurrence occurred at a similar rate in patients treated with DAA or IFN regimens after adjustment of the cofactors [61, 63, 64]. The cumulative incidence of HCC recurrence was dependent on the achievement of SVR in both arms of treatment [63]. Moreover, in a study including 149 liver-transplanted candidates who underwent initial complete response to loco-regional therapies for HCV-related HCC, DAA therapy was associated with reduced risk of waitlist dropout due to tumor progression or death [65]. However, in a prospective cohort that included 333 successfully treated HCC patients, divided into 60 patients who received DAAs and 273 patients who were DAA-untreated after HCC ablation, a higher risk of HCC recurrence appeared in post-DAA-treated patients versus

untreated patients. In addition, the risk was higher in patients treated with transarterial chemoembolization rather than curative measures. The main cofounders affecting HCC recurrence were age, male gender, mean tumor size, and the time interval between complete HCC ablation and occurrence of HCC recurrence [66].

Fibrosis regression and the risk of HCC

In a study by Crissien et al. five patients developed HCC after SVR over the emerging 5 years; two of them experienced fibrosis regression by TE [67]. In addition, Chekuri et al. suggested that fibrosis regression reached its plateau about 1 year after SVR [68]. Moreover, the fibrosis regression does not exclude the development of HCC years after treatment [67, 68]. Therefore, due to the lack of sufficient information about the possible risk of HCC reduction after SVR with the DAAs, patients, particularly with advanced fibrosis namely F3/F4, should undergo a regular screening of HCC [69].

Conclusions

DAA regimens represent a breakthrough of this century. DAAs have demonstrated genuine significant impacts on all HCV-related health hazards, initially sourced from liver fibrosis regression which is considered the milestone of chronic liver disease with its complications. It was assumed that the more time passed, the more significant reported changes on fibrosis appeared. However, DAAs have proved high accuracy in the early distinguishing of dynamic fibrosis regression changes. However, proper judging on the effect of DAA therapies of HCV on liver disease burden should be more furtherly evaluated on large-scale cohorts, along with longer durations. The unmet need of a single reproductive test equating the accuracy of liver biopsy for evaluating fibrosis rather than necroinflammation should be the urge of upcoming research.

Abbreviations

ARFI: Acoustic radiation force impulse elastography; CPA: Collagen proportionate area; DAAs: Direct-acting antiviral regimens; EOT: End of treatment; HAI: Histology activity index; HCV: Hepatitis C virus; LS: Liver stiffness; MRE: Magnetic resonance elastography; P-I-R Score: Progressive, indeterminate, and regressive score; SHG/TPEF: Second harmonic generation/two-photon excitation fluorescence; SVR: Sustained virological response; SW: Shear wave; TE: Transient elastography; HCC: Hepatocellular carcinoma

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Competing interests

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