Clinical and Experimental HEPATOLOGY

Clin Exp HEPATOL 2017; 3, 4: 181-186
DOI: https://doi.org/10.5114/ceh.2017.71491
Received: 06.08.2017, **Accepted:** 03.09.2017, **Published:** 16.11.2017

Review paper

Hepatitis C is now curable, but what happens with cirrhosis and portal hypertension afterwards?

Ivica Grgurevic[1,2], Tonci Bozin[1], Anita Madir[2]

[1]Department of Gastroenterology, Hepatology and Clinical Nutrition, University Hospital Dubrava, Zagreb, Croatia
[2]University of Zagreb School of Medicine, Zagreb, Croatia

Abstract

Results from the interferon era have demonstrated reversibility of cirrhosis following viral eradication, but only for patients in the initial stage of cirrhosis. Although direct-acting antivirals (DAA) represent revolutionary treatment of hepatitis C, there are currently no studies showing histological effects of therapy on a large number of cirrhotic patients. However, studies involving transient elastography demonstrated a rapid decrease in liver stiffness after successful DAA therapy, probably due to resolution of inflammation, rather than fibrosis regression, as the latter requires a longer period of time. Reversal of fibrosis and cirrhosis upon viral eradication is a prerequisite for the reduction of portal pressure, but this effect has only been observed for the subclinical stage of portal hypertension (PH). On the other hand, the majority of patients with clinically significant PH remain at risk of decompensation and death, despite hepatitis C virus cure, as PH remains high in this setting. This calls for novel therapeutic approaches.

Key words: hepatitis C, interferon, direct-acting antivirals, cirrhosis, portal hypertension.

Address for correspondence

Ivica Grgurevic, MD, PhD, Assist. Prof., Department of Gastroenterology, Hepatology and Clinical Nutrition, Department of Medicine, University Hospital Dubrava, University of Zagreb School of Medicine and Faculty of Pharmacy and Biochemistry, Avenija Gojka Suska 6, Zagreb 10 000, Croatia, phone: +385 1 290 3434, fax: +385 1 290 2550, e-mail: ivica.grgurevic@zg.htnet.hr

Introduction

The appearance of direct-acting antivirals (DAA) in 2011 marked the beginning of a new era in hepatitis C treatment. Since 2014, 'all-oral therapy' has been introduced, with nearly a 100% successful eradication rate for the hepatitis C virus (HCV) achieved, including cirrhotic patients [1]. It has been well documented that viral clearance upon receiving therapy generally results in reduced morbidity and mortality from chronic liver disease [2], but how this influences clinical outcomes in patients with already established cirrhosis and portal hypertension (PH), as the most endangered cohort, is a matter of debate. In other words, does the HCV cure translate into halting the progression of liver disease, and does it lead to the reversal of cirrhosis into lower histological stages and regression of PH? The theoretical background that allows for these issues to be addressed has only recently been established, characterized by the modern concept that views cirrhosis and PH as dynamic processes in the context of advanced chronic liver disease [3].

Fibrosis-cirrhosis-portal hypertension interrelationship

The results of numerous studies have led to a modern paradigm in which liver cirrhosis can no longer be considered as a single or static stage of liver disease [4-6]. Histologically, cirrhosis is defined by the abundance of fibrous tissue in the form of connective septa, which surround hepatic lobules, accompanied by the neovascularization of these septa, the capillarization of sinusoids and the formation of regenerative nodules. However, the amount of connective tissue may vary significantly depending on the aetiology and stage of the disease, which can be elegantly shown by a computer-assisted analysis of histological slides stained via

the Picro-Sirius Red method [7]. When this method is used, collagen is stained red while the rest of the liver tissue remains yellow; the percentage (%) of the red-stained area over the analysed field can be calculated, representing the relative proportion of collagen. By using this approach, the amount of collagen has been reported to vary from 9 to 62% in patients with liver cirrhosis [7, 8]. It is logical to expect that a patient with a greater amount of connective tissue has poorer liver functioning, higher portal pressure and a worse prognosis compared to a patient in the initial stage of cirrhosis with less connective tissue in the liver [9]. Indeed, patients with thicker connective septa in the liver have significantly higher PH, as expressed by the hepatic venous pressure gradient (HVPG) [10]. Changes that take place at the tissue and haemodynamic level translate into clinically visible signs and events, which have proved useful when discriminating between cirrhotic patients in terms of disease severity and prognosis, with both significantly influenced by the presence and severity of PH and its complications [3, 5]. Thus, patients with compensated cirrhosis can be further subclassified into stage 1 (with no oesophageal varices [OVs] or ascites) and stage 2 (with OVs but no ascites). Patients with decompensated cirrhosis can be subclassified into stage 3 (with ascites as a decompensating event, but no bleeding from OVs), and stage 4 (with bleeding from OVs with or without ascites). Between these stages, there is a significant difference in survival: one-year mortality is 1% for stage 1, 3% for stage 2, 20% for stage 3 and 57% for stage 4 [11]. These clinical categories can be even more accurately described by continuous variables that better reflect the evolution of histological changes and the increase in portal pressure. It has been accepted that liver stiffness (LS), measured by transient elastography (TE) or other elastographic methods, increases with deterioration during the clinical stage of liver cirrhosis, caused by increased accumulation and changes in the structure of the connective tissue [12]. On the other hand, the continuous increase of portal pressure with the worsening of the cirrhosis can be tracked by HVPG measurement. PH expressed by the HVPG has been demonstrated as the best predictor of decompensation in patients with compensated cirrhosis, even better than the Child-Pugh score, the MELD score and serum albumin concentrations [13].

Therefore, if PH is that important to the clinical outcomes of patients with advanced liver disease, and if PH (at least in the initial stage) results mainly from the accumulation of connective tissue and other architectural derangements within the liver, it very important to understand whether cirrhosis, as the underlying condition for PH, is reversible upon aetiological treatment (HCV eradication, for example), and whether this reversal leads to PH regression [14].

Cirrhosis reversibility by interferon-based treatment regimens

Most data on cirrhosis reversibility in the setting of chronic hepatitis C have been generated during studies that analysed the effect of interferon-based treatment regimens. In a meta-analysis that included six studies with a total of 443 patients with HCV cirrhosis treated with interferon and ribavirin, a sustained viral response (SVR) was achieved in 31% of the patients, with histological regression of cirrhosis observed in 51% of these [15]. It has been demonstrated that the proportion of patients with cirrhosis regression depends on the time between the two liver biopsies. Thus, the relative risk of cirrhosis regression was found to be 4.33 (CI = 1.1-17.0, $p = 0.04$) in patients with > 36 months between the follow-up and the initial (pre-therapeutic) liver biopsy, whereas it was 1.79 (CI = 1.26-2.29, $p < 0.01$) in patients who had a shorter interval, indicating that the regression of cirrhosis is a slow process [15]. Another important notion emerging from interferon era studies is that achieving an SVR is the most important predictor of cirrhosis reversibility. Specifically, in a study that analysed 3,010 HCV patients (153 with cirrhosis, median interval 20 months between the biopsies) treated with different regimens of conventional or PEG-interferon ± ribavirin, reversibility of cirrhosis was observed in 49% of patients who achieved an SVR, with an average METAVIR stage 1.9 in the follow-up biopsy [16]. In patients with a histologically confirmed reversion of cirrhosis, the SVR was 33%, as compared to 15% in patients who remained cirrhotic ($p = 0.01$). In multivariate logistic regression, the SVR was the only factor associated with cirrhosis reversibility (OR = 0.39; 95% CI = 0.17-0.85; $p = 0.02$). However, to address the final clinical and epidemiological impact of the SVR, as achieved by interferon-based therapy, it is important to explore its effects in terms of preventing the development of new cases of liver cirrhosis, thus reducing the adverse clinical outcomes of chronic hepatitis C. The answer to this was presented in a French study involving 933 patients with chronic hepatitis C (64% were treated with interferon regimens) who were subjected to liver fibrosis tests (Fibrotest or Fibroscan or liver biopsy) conducted at a 6.3-year interval (median) [17]. An SVR was achieved in 28.7% (171 out of 595 treated) of the patients, while cirrhosis regressed in 56% (24 out of 43) of the SVR patients. However, during the follow-up period, 15 (11.7%) new cases of

cirrhosis were observed in the SVR patients, meaning that the net effect of therapy was a modest 5% (24 patients with regression of cirrhosis minus 15 patients with newly developed cirrhosis, i.e., 9 patients) in terms of the overall reduction of cirrhosis development following the SVR [17]. To conclude, interferon-based therapy resulted in a 30% rate of SVR among patients with HCV cirrhosis, of whom 50% experienced regression of cirrhosis. However, due to new cases of cirrhosis in patients with an SVR, the net reduction of newly developed cirrhosis was a disappointing 5%. This leads to the conclusion that therapy should be started as soon as possible, preferably before the advanced fibrosis develops. In the future, patients with advanced liver fibrosis (METAVIR F3-F4) could hypothetically benefit from adding potential antifibrotic drugs (currently in development) to the aetiological treatment in order to prevent the progression of fibrosis, thus preventing the development of cirrhosis, PH and adverse clinical outcomes. This remains speculative for now and should be tested when (and if) these new drugs become available.

Cirrhosis reversibility by direct-acting antivirals

Data on cirrhosis reversibility in patients treated with DAA are scarce and based mainly on studies in which TE was used for fibrosis staging. Given that liver biopsy is nowadays rarely used to evaluate fibrosis in patients with chronic hepatitis C, it is not possible to determine with certainty the number of patients that actually had a reversion of histological changes, which is typical for cirrhosis as a distinctive stage of liver disease. Based on data from the interferon era, LS, as assessed by TE, has been demonstrated to be insufficiently reliable in defining the fibrosis stage following antiviral treatment. In a study by D'Ambrosio *et al*., patients with HCV cirrhosis were monitored for five years following an SVR and then had a control liver biopsy and LS measurements performed [18]. Histological regression of cirrhosis was observed in 20/33 (61%) patients, whereas LS < 12 kPa, which is considered a reliable cut-off value to rule out cirrhosis, was measured in 24/33 (73%) patients. Although within the range of LS that is not indicative of cirrhosis, 5 out of these 24 patients (21%) had cirrhosis as demonstrated histologically [18]. These results lead to the conclusion that TE cut-off values used for fibrosis staging in patients with chronic hepatitis C are not applicable for patients following viral eradication and should probably be lower. Given that LS measurements in viraemic patients, beside fibrosis, also include the inflammatory infiltrate component, after eradication of the virus and resolution of the inflammation, a rapid decrease in liver stiffness is expected, but the regression of fibrosis is a much longer process. For these reasons, current data on cirrhosis reversibility after DAA therapy are of limited value, since they are based mostly on indirect indicators of liver fibrosis, such as LS measurements. For example, in a study by Pineda *et al*., among 49 patients with pre-therapeutic LS values indicating cirrhosis (> 12.5 kPa), LS decreased to values that would indicate cirrhosis reversal (< 12.5 kPa) in 12 (24%) patients after reaching an SVR12 following DAA therapy [19]. In another study in which 392 patients with chronic hepatitis C were treated with DAA, regression of LS was noted, from an average of 12.65 kPa prior to therapy to 8.55 kPa 40 weeks after achieving an SVR, which is a reduction of 32% ($p < 0.001$); meanwhile, the FIB4 score regressed from 2.5 to 1.8 [20]. Since liver biopsy was not used in this study, the authors were unable to provide histological data to support cirrhosis regression. Similar results were obtained in a study by Romanian authors, in which 225 patients with HCV cirrhosis (all genotype 1b) were treated with DAA for 12 weeks, with LS analysed before treatment, at the end of treatment (EOT) and 12 weeks after that (SVR12) [21]. In these patients, a progressive decrease in LS was noted, from the pre-therapeutic 26.4 kPa to 23.5 kPa at the EOT, to a final 21.3 kPa in SVR12, which is a reduction of 20% ($p < 0.001$), again without histological data provided. Attempts to reach conclusions on cirrhosis reversibility upon DAA treatment, assessed by non-invasive methods, as represented by TE, proved misleading, according to data that were recently published by an American group of authors. They investigated the effects of DAA in a group of 100 patients with advanced HCV fibrosis or cirrhosis (35 with F3 and 65 with F4 METAVIR stages) [22]. Again, the improvement of LS was observed in 55% of the patients, which occurred after an average of 2.8 years of follow-up. However, among 10 patients in whom baseline and follow-up liver biopsy was performed in addition to TE, 4/9 patients with final LS values of < 9.5 kPa (which would be indicative of a stage < F3) still had F3 or F4 stage fibrosis at the follow-up biopsy, revealing the erroneous results of TE in 44% of patients in this setting.

Reversibility of portal hypertension by interferon-based treatment regimens

The effect of antiviral therapy on PH and the clinical outcomes of patients were analysed in a study by Italian authors, which included patients with compensated HCV cirrhosis who were treated with PEGylated

interferon and ribavirin [23]. The patients were divided into stage 1 (no OVs and no ascites) and stage 2 (with OVs but no ascites). SVR achievement at stage 1 cirrhosis resulted in a significantly lower number (but not complete prevention) of newly developed OVs, compared to patients who did not achieve an SVR. However, in the group of patients with stage 2 cirrhosis, there was no difference in the endoscopic stages of OVs at follow-up, regardless of the SVR status. These results indicate that HCV eradication can significantly prevent development and aggravation of PH in patients at an early stage of cirrhosis with subclinical PH (who have not yet developed OVs). However, in the setting of cirrhosis with clinically significant PH (CSPH) (which is, by definition, present in patients with OVs), eradication of the infection seems not to have the potential to prevent PH progression. In the same study, the authors found that cirrhosis decompensation was completely prevented in patients with stage 1 cirrhosis, while the patients in stage 2 who achieved an SVR had a significantly lower risk of decompensation compared to patients in whom the HCV was not eradicated. These results indicate that HCV eradication is an effective way of preventing the development of CSPH and OVs, but only in patients treated in the early stages of the disease (stage 1 cirrhosis, without OVs and ascites), which once again validates the above-mentioned conclusion that patients need to be recognized and treated as early as possible.

Reversibility of portal hypertension by direct-acting antivirals

Given the relatively short period since DAA were introduced, data on their effect on PH are relatively scarce. In one of the first pioneering studies, published in 2015, Afdhal *et al*. analysed the effect of DAA (sofosbuvir + ribavirin for 48 weeks) on 50 patients with HCV cirrhosis and PH (all had HVPG ≥ 6 mmHg) [24]. An SVR was achieved in 72% of patients, while paired (before and after therapy) HVPG measurements were performed on 37 patients. For 33 patients who were included in the final analysis, the mean HVPG was reduced by 0.5 mmHg, the MELD score decreased by 1.6 points and the Child-Pugh class regressed from B to A in 69% of patients. The HVPG decreased in 20/33 patients (8/33 for ≥ 20% compared to initial values), remained unchanged in 2 patients and worsened in 13 patients after therapy. In the multivariate analysis, a higher initial MELD score was associated with a greater HVPG reduction at the follow-up stage. A group of authors from Barcelona presented results on the effect of DAA on PH in 118 patients with HCV cirrhosis and CSPH (92% were at Child-Pugh stage A, and 80% had OVs, of whom 40% had large varices), of which 31% had at least one episode of previous decompensation (14% variceal bleeding, 21% ascites) [25]. Upon achieving an SVR, the HVPG decreased from the pre-therapeutic 16.4 ± 4.5 mmHg to 14.5 ± 4.6 mmHg (mean decrease –1.9 ± 3, $p < 0.01$). A clinically relevant reduction in the HVPG (≥ 10%) was observed in 65 (54%) patients (with a reduction of ≥ 20% observed in 34% of the patients). However, CSPH persisted after achieving an SVR in as many as 86% of the patients. These results allow us to conclude that CSPH persists in the majority of patients treated with DAA despite achieving an SVR, meaning that they remain at risk of PH progression and cirrhosis decompensation. Similar results were also reported by a group of authors from Vienna who analysed the effect of DAA on 104 patients with chronic hepatitis C and PH (all had HVPG ≥ 6 mmHg prior to therapy) [26]. An SVR was achieved in 100 (96%) patients, 60 of whom underwent follow-up HVPG control measurements. There was a decrease in the HVPG from the pre-therapeutic 13.1 ± 0.7 mmHg to 10.4 ± 0.79 mmHg after achieving an SVR, which represents an average decrease of 2.63 ± 0.38 mmHg or 23 ± 2.9% ($p < 0.001$). In patients with a pre-therapeutic subclinical PH (HVPG 6-9 mmHg), portal pressure normalized (HVPG < 6 mmHg) in 63% of patients; no progression of HVPG to ≥ 10 mmHg was observed. In patients with CSPH before treatment, a clinically relevant reduction of HVPG > 10% was observed in 63%; however, the HVPG decreased to < 10 mmHg in only 24% of patients. The results of this study confirm the efficacy of DAA in treating PH in patients in the early stages of liver disease who have subclinical PH. However, in patients with already existing CSPH, despite achieving an SVR, CSPH persists in 76% of patients, meaning that they remain at risk of developing adverse outcomes.

Conclusion and perspectives

Results from the interferon era demonstrate cirrhosis reversibility in the lower histological stages upon HCV eradication, although it is important to bear in mind that these data refer to compensated patients at the initial stage of cirrhosis. However, viral eradication does not stop the progression of fibrosis and the development of cirrhosis in every patient, as the interferon-based regimens seem to prevent the development of cirrhosis in only 5% of treated patients over a 10-year period. This suggests that patients with advanced liver fibrosis (F3-F4 according to METAVIR) could be considered as potential candidates for antifibrotic regimens (cur-

rently under development), in addition to aetiological treatment, in order to prevent progression to cirrhosis, PH and adverse clinical outcomes. For this approach, reliable and safe antifibrotic drugs are awaited, as well as criteria to recognize patients at risk of fibrosis progression. Although DAA represent a revolution in hepatitis C treatment, there are currently no studies to show their actual histological effects on a larger cohort of patients. The results of fibrosis assessment by non-invasive methods (TE) indicate a significant and rapid decrease in LS upon successful therapy, which is probably due to the resolution of inflammation, rather than fibrosis regression, which requires a longer period of time. LS values obtained by TE, as used in the diagnostic work-up of viraemic hepatitis C patients, have been proven to be unreliable upon the eradication of the HCV and the resolution of inflammation. As such, further research is needed to define the optimal values in this clinical setting. However, taking into account regressive LS dynamics and histological results in patients who achieved an SVR using interferon regimens, at least the same proportion of cirrhosis reversibility may be expected in patients who achieve an SVR using DAA. Early PH mainly results from increased resistance to the blood flow within the liver, largely caused by the accumulation of connective tissue and liver architectural derangements. Therefore, treatment options (both interferon-based and DAA), which resulted in the reversion of cirrhosis and the regression of fibrosis upon viral eradication, have been accompanied by a reduction in portal pressure in the early (subclinical) stage of PH. However, although viral eradication by DAA can be achieved in a large number of patients with cirrhosis and CSPH as well, PH remains within a clinically significant range in the majority (76-86%) of patients, thus exposing them to the risk of decompensation and death, even after achieving an SVR. This again raises the question about the possible use of drugs (statins, for example), in addition to aetiological treatment, which could further influence the reduction of PH, even after achieving an SVR. It remains to be seen which patients would be potential candidates for such an approach. According to the current literature, all patients with CSPH prior to therapy (measured by the HVPG or the existence of OVs) could be candidates. In patients without CSPH and OVs, further research should be carried out in order to define those at risk of PH progression, despite achieving eradication of the HCV.

Disclosure

Authors report no conflict of interest.

References

1. Zeuzem S. Treatment Options in Hepatitis C. The Current State of the Art. Dtsch Arztebl Int 2017; 114: 11-21.
2. Simmons B, Saleem J, Heath K, et al. Long-Term Treatment Outcomes of Patients Infected With Hepatitis C Virus: A Systematic Review and Meta-analysis of the Survival Benefit of Achieving a Sustained Virological Response. Clin Infect Dis 2015; 61: 730-740.
3. Garcia-Tsao G, Friedman S, Iredale J, et al. Now there are many (stages) where before there was one: In search of a pathophysiological classification of cirrhosis. Hepatology 2010; 51: 1445-1449.
4. Germani G, Burroughs AK, Dhillon AP. The relationship between liver disease stage and liver fibrosis: a tangled web. Histopathology 2010; 57: 773-784.
5. Rosselli M, MacNaughtan J, Jalan R, et al. Beyond scoring: a modern interpretation of disease progression in chronic liver disease. Gut 2013; 62: 1234-1241.
6. Hytiroglou P, Snover DC, Alves V, et al. Beyond "cirrhosis" a proposal from the international Liver Pathology Study Group. Am J Clin Pathol 2012; 137: 5-9.
7. Manousou P, Dhillon AP, Isgro G, et al. Digital image analysis of liver collagen predicts clinical outcome of recurrent hepatitis C virus 1 year after liver transplantation. Liver Transpl 2011; 17: 178-188.
8. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet 2014; 383: 1749-1761.
9. Khan MH, Farrell GC, Byth K, et al. Which patients with hepatitis C develop liver complications? Hepatology 2000; 31: 513-520.
10. Kumar M, Sakhuja P, Kumar A, et al. Histological subclassification of cirrhosis based on histological–haemodynamic correlation. Aliment Pharmacol Ther 2008; 27: 771-779.
11. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006; 44: 217-231.
12. Berzigotti A. Non-invasive evaluation of portal hypertension using ultrasound elastography. J Hepatol 2017; 67: 399-411.
13. Ripoll C, Groszmann R, Garcia-Tsao G, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology 2007; 133: 481-488.
14. Pinzani M, Vizzutti F. Fibrosis and cirrhosis reversibility: clinical features and implications. Clin Liver Dis 2008; 12: 901-913.
15. Akhtar E, Manne V, Saab S. Cirrhosis regression in hepatitis C patients with sustained virological response after antiviral therapy: a meta-analysis. Liver Int 2015; 35: 30-36.
16. Poynard T, McHutchison J, Manns M, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology 2002; 122: 1303-1313.
17. Poynard T, Moussalli J, Munteanu M, et al. Slow regression of liver fibrosis presumed by repeated biomarkers after virological cure in patients with chronic hepatitis C. J Hepatol 2013; 59: 675-683.
18. D'Ambrosio R, Aghemo A, Fraquelli M, et al. The diagnostic accuracy of Fibroscan® for cirrhosis is influenced by liver morphometry in HCV patients with a sustained virological response. J Hepatol 2013; 59: 251-256.
19. Pineda JA, Merchante N, Mancebo M, et al. Short-term effect of DAA IFN-free regimens on liver stiffness. J Hepatol 2017; 66: S525.
20. Bachofner JA, Valli PV, Kroger A, et al. Direct antiviral agent treatment of chronic hepatitis C results in rapid regression of transient elastography and fibrosis markers fibrosis-4 score and aspartate aminotransferase-platelet ratio index. Liver Int 2017; 37: 369-376.

21. Sporea I, Lupușoru R, Mare R, et al. Dynamics of liver stiffness values by means of transient elastography in patients with HCV liver cirrhosis undergoing interferon free treatment. J Gastrointestin Liver Dis 2017; 26: 145.
22. Pockros P, Crissien-Martinez AM, Frenette C, et al. Degree of liver fibrosis regression predicted by transient elastography after cure of chronic hepatitis C with direct acting antivirals is overestimated but confirmed by liver biopsy. J Hepatol 2017; 66: S108.
23. Di Marco V, Calvaruso V, Ferraro D, et al. Effects of eradicating hepatitis C virus infection in patients with cirrhosis differ with stage of portal hypertension. Gastroenterology 2016; 151: 130-139.
24. Afdhal N, Everson GT, Calleja JL, et al. LP13: Effect of long term viral suppression with sofosbuvir + ribavirin on hepatic venous pressure gradient in HCV-infected patients with cirrhosis and portal hypertension. J Hepatol 2015; 62: S269-S270.
25. Lens S, Alvarado-Tapias E, Marino Z, et al. Impact of all-oral antiviral therapy on portal pressure and hemodynamics on HCV-infected cirrhotic patients. Hepatology 2016; 64 (Suppl 1): A58.
26. Mandorfer M, Kozbial K, Schwabl P, et al. Sustained virologic response to interferon-free therapies ameliorates HCV-induced portal hypertension. J Hepatol 2016; 65: 692-699.