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Impact of hepatitis C oral therapy in portal hypertension

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Abstract

Chronic hepatitis C is a leading cause of morbidity and

mortality, mainly related to fibrosis/cirrhosis and portal hypertension. Direct antiviral agents are highly effective and safe and can now cure > 90% of the patients. Sustained viral response (SVR) after interferon-based regimens has been associated with improvement in liver function, fibrosis and portal hypertension in a significant proportion of patients, although a point of no return seems to exist from which viral elimination is no longer capable of preventing portal hypertension progression and liver decompensation. Indeed, although SVR is associated with improvement of hepatic venous pressure gradients and therefore a decreased risk of *de novo* esophageal varices, several studies show that viral clearance does not eliminate the risk of variceal progression, liver decompensation and death in patients with pre-established portal hypertension. Although evidence about the effects of direct antiviral agents (DAAs) on clinically significant outcomes is still scarce and with short follow-up, DAAs can decrease the burden of the disease if patients are timely treated before significant fibrosis and portal hypertension develops. Studies with longer follow-up are awaited to establish the real magnitude of hepatitis C treatment on portal hypertension. Future studies should also focus on predictors of portal hypertension resolution since it can influence management and avoid unnecessary monitoring

Key words: Hepatitis C; Portal hypertension; Direct antiviral agents; Cirrhosis; Fibrosis; Interferon

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Core tip: Hepatitis C is associated with significant morbidity and mortality, mainly through portal hypertension complications. Hepatitis C treatment is associated with improvement of liver function and fibrosis, better quality of life and reduced mortality. The knowledge of the impact of viral clearance on portal hypertension is also relevant because it greatly influences clinical outcomes and can influence management after treatment. Several studies show

that the benefits on portal hypertension are higher if treatment is delivered before clinically significant portal hypertension is developed, encouraging timely and early treatment with the highly efficacious and safe direct antiviral agents.

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INTRODUCTION

Chronic hepatitis C is a leading cause of morbidity and mortality worldwide mainly due to complications of cirrhosis, portal hypertension and hepatocellular carcinoma. Hypertensive bleeding is the most significant complication of portal hypertension, being associated with a high early mortality (20% at 6 wk)^[1]. Mortality attributed to viral hepatitis has been increasing in the last decades and viral hepatitis was the seventh leading cause of death worldwide in 2013^[2].

Direct antiviral agents (DAAs) are highly effective and safe and are changing the prognosis and burden of the disease. Sustained virologic response (SVR) is now achieved in > 90% of the patients and is associated with improvements in liver function, fibrosis and overall survival. Portal hypertension is also expected to improve with virological response, paralleling the improvements in liver inflammation and liver fibrosis. Liver transplantation due to viral hepatitis C can also decrease in the next years^[3]. The knowledge of the effects of hepatitis C virus (HCV) elimination on clinically significant outcomes like portal hypertension and its complications is thus of unremarkable importance since it can influence management after SVR and is the focus of this report.

IMPACT OF SVR IN PORTAL HYPERTENSION BEFORE DAAs

Prior to DAAs development HCV treatment was mainly recommended in patients with advanced fibrosis or cirrhosis, in order to balance treatment benefits with the risk of liver complications and treatment adverse events. SVR was achieved in 40%-60% of cases with interferon (INF) based therapies and was associated with improvements in liver fibrosis, portal hypertension, liver-related adverse events, liver-related mortality, overall mortality and decreased HCC incidence^[4-7]. HCV therapy was also associated with quality of life improvement, namely reducing decompensation and hospitalization rates^[8,9].

Liver fibrosis, a major determinant of portal

hypertension, was shown to improve in several studies using paired liver biopsies^[10-13] and non-invasive biomarkers^[12,14]. However, a "point of no return" seems to exist for both liver fibrosis, liver function and portal hypertension. Indeed, in a large cohort of INF-treated patients, 740/1094 (68%) of the patients who achieved SVR maintained fibrosis stage 20 mo after treatment and fibrosis improved in only 277/1094 (25%)^[10].

Concerning portal hypertension, SVR was associated with a statistically significant yet modest decrease in hepatic venous pressure gradient (HVPG) 6 mo after INF-based therapy^[15]. In a small study including 8 patients who achieved SVR with antiviral triple therapy there was a significant decrease in both HVPG and liver stiffness 24 wk after therapy (10.3 mmHg vs 6.1 mmHg and 21.3 kPa vs 6.4 kPa, $P < 0.001$), with 5 patients (62.5%) achieving an HVPG < 6 mmHg^[16]. Indirect markers of portal hypertension such as platelet count^[17-19] and spleen size^[17] were also shown to improve after HCV eradication in INF-treated cirrhotic patients.

Concerning clinical endpoints after HCV eradication, a prospective study with 12 years follow-up showed a lower incidence of esophageal varices in Child A cirrhotic patients with SVR (0% vs 32%-39% in the untreated/non-SVR group)^[20]. A lower incidence of *de novo* esophageal varices was also reported in cirrhotic patients who achieved SVR, although the progression of variceal size was not statistically different in patients with and without SVR^[21], supporting the concept of the point of no return. Another prospective study by Di Marco *et al*^[22] also showed that SVR was associated with a lower incidence of *de novo* esophageal varices in cirrhotic patients treated with PEG-INF and ribavirin (HR = 0.23, 95%CI: 0.11-0.48), although it was not associated with a decrease in variceal progression or liver decompensation in those with pre-existing varices^[22].

Petta *et al*^[23] also reported a reduced incidence of *de novo* esophageal varices in patients with SVR (3.4% vs 37.4%) On the other hand, although SVR was associated with a decrease in liver decompensation and mortality at 10 years, patients with esophageal varices at baseline had an increased risk of decompensation and death. Further supporting these findings, Lens *et al*^[24] recently reported that cirrhotic patients with clinically significant portal hypertension at baseline remain at risk for liver decompensation after 5 years, regardless of SVR. In these study, although SVR was associated with a non-statistically significant decrease in HVPG, a higher baseline HVPG was found as the only predictor of liver decompensation at multivariate analysis.

Besides the absence of improvement in HVPG, other factors may also influence the development of complications of portal hypertension after SVR. Indeed, Nagaoki *et al*^[25] reported that portosystemic collateral shunts at baseline (assessed by CT) were associated

with exacerbation of esophageal varices and hepatic encephalopathy after SVR. Cofactors for liver disease such as obesity, alcohol consumption and hepatitis B may also contribute to minor improvement in portal hypertension after HCV eradication.

IMPACT OF SVR IN PORTAL HYPERTENSION WITH DAAs

In order to accomplish the goal of HCV elimination as an important health public threat by 2030^[26], HCV treatment is nowadays recommended in almost all infected patients, even those without significant fibrosis^[27]. This, together with the high SVR rates and the safety profile of DAAs, can change the history of HCV infection and improve clinical outcomes namely avoiding the development of portal hypertension and its improvement in patients with patients with established portal hypertension.

Liver fibrosis has also been shown to improve after INF-free DAA treatments, based on serum fibrosis biomarkers^[28,29] and transient elastography^[29,30]. SVR, liver function and fibrosis are undoubtedly important endpoints to assess the efficacy of HCV treatment, although portal hypertension and its complications (*i.e.*, liver decompensation and liver-related mortality) may be more adequate to assess treatment effectiveness. In fact, the knowledge of the impact of DAA treatments in portal hypertension and cirrhosis complications may influence patient management after achieving SVR. Due to the novelty of DAA INF-free therapies (and thus short follow up times) there are only few studies assessing the effects of HCV novel treatments on portal hypertension and clinical decompensation.

In patients successfully treated with DAAs, fibrosis and MELD score were shown to improve^[31-33]. The decrease in necroinflammation along with fibrosis improvement can decrease intrahepatic resistance and thus portal pressure. In particular, improvement of liver inflammation, aminotransferases and liver function early during treatment can explain the rapid decreases in HVPG and liver stiffness that were found in some studies.

A well designed retrospective study conducted by the Austrian group evaluated the changes in HVPG and liver stiffness in 60 cirrhotic patients (84% Child A) treated with various combinations of DAAs^[34]. SVR led to a reduction in HVPG in 80% of the patients (mean HVPG change -2.63 ± 0.38 mmHg, $P < 0.001$). Importantly, in the subgroup of patients with clinically significant portal hypertension (≥ 12 mmHg) at baseline, 63% achieved a HVPG decrease $\geq 10\%$ and a decrease $> 20\%$ or to < 12 mmHg was found in 51%, at a median of 114 d after treatment. This beneficial effect was found in all strata of HVPG, although portal hypertension was less likely to improve in Child B patients. Liver stiffness and platelet counts improvements were also associated with SVR.

In another study including 33 cirrhotic patients treated with 48 wk sofosbuvir + ribavirin with clinically significant portal hypertension at baseline, 24% achieved a $\geq 20\%$ decrease in HVPG at the end of treatment, although the median HVPG change in the entire cohort was modest (-0.5 mmHg)^[35]. Interestingly, higher baseline MELD score was associated with a higher HVPG response ($P = 0.04$). Longer follow-up results of this trial are waited since the full effects of SVR on architectural changes and fibrosis improvement may have their effects later on time. Indeed, a more pronounced liver stiffness improvement was found between baseline and end of treatment than between end of treatment and 6 mo after, suggesting an important role of necroinflammation on the early improvements in liver stiffness^[36]. Deterding *et al.*^[37] suggested a two-phasic decline of portal hypertension consisting of a first rapid phase during treatment (associated with improved inflammation) followed by a slower second phase after 6-12 mo (associated with fibrosis regression). This hypothesis will surely be tested and hopefully confirmed when longer follow-up results become available.

The results of the few studies evaluating the changes in portal hypertension shortly after DAA treatment thus suggest that portal hypertension improves quickly during and after HCV eradication, which can lead to improvements in clinically significant outcomes such as variceal bleeding, ascites and encephalopathy. This theoretical concept can favor the treatment of patients with decompensated cirrhosis in whom INF-treatments were previously contraindicated. However, treatment in this setting is still a matter of debate. Indeed, although HCV eradication can decrease Child-Pugh and MELD scores in a subset of patients (decreasing the need of liver transplantation), it does not necessarily improve liver function and portal hypertension sufficiently to the point of a compensated patient with a functional live and the need for liver transplantation may persist but be delayed due to the MELD decrease (MELD purgatory).

CONCLUSION

The available evidence shows that HCV eradication with both INF-based and DAA INF-free therapies can improve liver fibrosis and portal hypertension. The evidence of portal hypertension improvement with DAAs is still scarce but consistent with a rapid and significant improvement, which can also improve clinically significant outcomes such as variceal bleeding. However, data suggest that a point of no return exist, encouraging early treatment before the development of significant fibrosis and portal hypertension. DAA therapy, with its extremely high efficacy and safety profile, have an undoubtedly important role since it allows the cure of almost all infected patients, preventing fibrosis and portal hypertension and improving clinical outcomes.

As we have seen, patients with established portal hypertension can improve although for now there are no data about the long term effects of DAAs. The available evidence is mainly based on retrospective studies with heterogeneous populations and endpoints definitions. As randomized controlled trials with active treatment and control groups are not ethically acceptable at this time point, the best studies to answer these unsolved questions are prospective studies with well-defined inclusion and exclusion criteria, well-defined clinically significant endpoints and with long follow-up. We suggest that further studies include patients along the spectrum of HCV infection (from asymptomatic with minimal liver damage to cirrhotic patients) with stratification according to the stage of liver disease (ideally evaluated by non-invasive methods validated in HCV infection such as elastography and non-invasive markers of fibrosis). Additionally, the assessed endpoints should be clinically significant and well defined (*e.g.*, variceal enlargement from small to large varices, *de novo* ascites, encephalopathy and hypersplenism) and follow-up should be longer than 5 years to evaluate the true impact of HCV treatment according to the stage of liver damage. Data collection should include an adequate characterization of disease stage at the beginning and at the end of follow-up (including aminotransferases, platelet count, ultrasound findings, liver stiffness, presence of ascites, varices and encephalopathy). These studies should then assess the treatment effects according to the stage of liver disease and should compare patients who achieve SVR with patients in whom these endpoint is not achieved.

Future studies should also focus on predictors of portal hypertension resolution since it can influence management and avoid unnecessary monitoring in the subset of patients with a very low probability of having clinically significant portal hypertension after treatment. Evaluation of molecular markers of extracellular matrix and hepatic stellate cell remodeling such as hyaluronic acid or alpha-2 macroglobulin may also have an investigational interest to assess if they can be a surrogate marker of the point of no return. The role of pre-existing significant porto-systemic shunts should also be evaluated.

Until the answers to these questions are available, screening for varices is still recommended in cirrhotic patients although recent Baveno VI consensus suggest that patients with Fibroscan® < 20 kPa and platelet count above 150000/μL can avoid screening endoscopy^[38]. In patients who undergo screening endoscopy and no varices are found, a follow-up screening after 3 years is still recommended if SVR was achieved and there are no cofactors (a 2 year interval is advised if there is ongoing liver injury).

Concerning patients with established portal hypertension and varices before treatment, the effects of SVR on variceal progression and on bleeding rates are also still unknown and should be evaluated in

future studies. For now, those with small varices who achieved SVR and without cofactors should undergo follow-up endoscopy in 2 years, while patients with large varices should undergo primary prophylaxis and adequate management^[38]. It should be also noticed that HCC surveillance should be continued in patients with F3 fibrosis or greater^[27].

In conclusion, the development of portal hypertension can be prevented and it can be improved in a significant proportion of patients as long as the treatment is delivered in a timely manner, before the point of no return. The long-term effects of DAAs on portal hypertension are not completely established and studies with longer follow-up are needed, but there is evidence from studies of the pre-DAA era that show significant benefits of SVR on portal hypertension, encouraging early treatment before significant fibrosis (F3/F4) and portal hypertension are established.

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