Chronic hepatitis C is the leading cause of advanced liver disease in the Western world. Most patients with liver cirrhosis develop portal hypertension (PHT) (i.e. an abnormal gradient between portal and inferior vena cava pressures), responsible for the most frequent and severe complications of liver disease and, as a consequence, the main cause of death and liver transplantation in those patients. The existence of a potential beneficial effect of antiviral therapy (AVT) on liver inflammation and fibrosis, partially independent of the degree of virological response, has been recently reported. However, the possible influence of these histological changes on PHT has not been evaluated. In this article, we summarize the available findings regarding the effect of AVT on PHT in patients with advanced chronic hepatitis C, as well as its possible implications for clinical practice and future avenues of investigation.

Keywords: hepatitis C, liver cirrhosis, hepatic venous pressure gradient, antiviral therapy

Introduction

It is clearly established that chronic hepatitis C virus infection (HCV) is the major cause of cirrhosis and its complications in the Western world. In addition, HCV cirrhosis is the main indication for liver transplantation, indicating the importance of advanced HCV chronic infection. The progression rate of chronic hepatitis C is variable but it is estimated that about 30% of patients progress to liver cirrhosis after 20 years of infection. The presence of cirrhosis implicates the distortion of liver architecture and the appearance of vascular abnormalities, both inducing an initial increase in intrahepatic vascular resistance that is followed by the appearance of multiple functional abnormalities in intrahepatic and splanchnic vascular beds. This complex setting leads to the development of portal hypertension (PHT), defined as the existence of an abnormal gradient between portal pressure and the pressure at the inferior vena cava. The degree of PHT is usually estimated by means of the hepatic venous pressure gradient (HVPG), which closely correlates with portacaval pressure gradient in both alcoholic and viral cirrhosis. Briefly, HVPG is calculated as the difference between the wedged hepatic venous pressure (equivalent to the portal vein pressure) and the free hepatic venous pressure (equivalent to the pressure in the inferior vena cava), and it is easily measured via hepatic vein catheterization with a balloon-catheter. Although increased resistance to portal blood flow related to morphological changes is the primary factor in the pathophysiology of PHT, the aforementioned functional component significantly contributes to aggravate and self-perpetuate the PHT syndrome. PHT plays a key role in the evolution of liver cirrhosis, as it is responsible for the more frequent and severe complications of cirrhosis: gastrointestinal bleeding from gastro-oesophageal varices, ascites, renal dysfunction and hepatic encephalopathy. Because of the combined impact of these complications, PHT represents the main cause of death and liver transplantation in patients with cirrhosis. HVPG has demonstrated its prognostic value in several clinical settings such as variceal formation or bleeding. On the other hand, a reduction in HVPG of at least 20% or below the 12 mm Hg threshold markedly reduces the risk of variceal bleeding and it is the current therapeutic goal in the management of PHT. Moreover, patients under pharmacological therapy who achieve this haemodynamic response have a significantly lower risk of developing ascites, hepatorenal syndrome, spontaneous bacterial peritonitis, hepatic encephalopathy and death during follow-up than non-responders. Therefore, PHT is a principal therapeutic objective in the management of chronic liver diseases. The low chance of sustained virological response (SVR) and the high risk of adverse events have limited in the past the use of antiviral therapy (AVT) in patients with HCV-related cirrhosis. However, as the combination of pegylated interferon and ribavirin has improved the likelihood of response up to 45% in cirrhotic patients without a significant increase in severe adverse events, currently available evidence suggests considering AVT in compensated cirrhosis. Although the principal aim of this AVT is to obtain an SVR, defined by the absence of viral replication 6 months after stopping therapy, several recent reports have suggested an additional beneficial effect of combined AVT on liver histology with a significant reduction in inflammation and fibrosis in addition to viral response. On the other hand, other physiological and pharmacological properties of interferon, besides its antiviral effect, may have an influence on liver inflammation and inflammatory mediators.

Does interferon improve portal hypertension?

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Introduction

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Therefore, it is possible to speculate about the potential role of interferon-based AVT in the pathophysiology of PHT.

In this review we analyse the available data regarding the possible effect of interferon-based AVT on PHT.

Does antiviral therapy decrease portal pressure?

As previously shown, several papers have clearly established that the increase in portal pressure has a central role in the development of complications of cirrhosis.3,12,13 The importance of portal pressure is also clearly demonstrated when analysing the existence of several threshold values of HVPG for the development of different manifestations of this syndrome. Thus, the decrease in HVPG is an important end-point when treatment of PHT is considered.

Only three studies have evaluated the effect of AVT on portal pressure.

The first of these studies evaluated the effect of 6 months isolated non-pegylated interferon administration on portal pressure in chronic hepatitis C cirrhotic patients.19 In this small placebo-controlled trial, end-of-treatment HVPG was significantly lower than baseline HVPG in interferon-treated patients, whereas it had increased in placebo-treated patients (Figure 1). Unfortunately, this study had to be interrupted because of the impossibility to include patients in the placebo group due to ethical considerations.

The second evidence regarding portal pressure decreasing effect of AVT comes from a sub-analysis of a large randomized placebo-controlled trial designed to evaluate the outcomes of cirrhotic patients who were administered isolated non-pegylated interferon for 6 months.20 Repeat measurements of the HVPG before and after treatment were only available in 10 of 99 patients, 5 in the active and 5 in the placebo arm. In this study no effects of AVT could be detected, probably due to the small sample size (Figure 2).

The last published study up to now was initially presented at the 2004 AASLD meeting in Boston.21 This is an open study in which blind evaluation of HVPG measurements performed immediately before and after a 24–48 month course of combined AVT according to HCV genotype was performed in 20 patients with compensated chronic hepatitis C, advanced liver fibrosis or cirrhosis, and PHT. The presence of PHT was assessed by an HVPG value greater than 5 mm Hg. Baseline and end-of-treatment liver biopsies were also done. Interestingly, a marked decrease in mean HVPG was observed after AVT (Figure 3); this effect was observed in all patients except one who underwent a sudden increase in ALT during therapy (Figure 4). The decrease in HVPG seemed to be mainly related to a decrease in inflammatory activity. In fact, the reduction of HVPG was greater in those patients with normal ALT at the end of therapy or with a reduction of at least two points in the histological score of inflammation. Moreover, those patients who achieved end-of-therapy virological response, who have consistently proven to be those with a more relevant improvement of liver inflammation after AVT, showed a greater reduction in PHT than non-responders. These findings are markedly different from those observed in a historical group of 30 HCV-compensated cirrhotic patients with a similar degree of PHT at baseline, in which two different haemodynamic studies were performed due to different reasons after a mean time period of 12 months. In this particular group, paired HVPG measurements showed a significant increase in portal pressure. In addition, only 10% of these patients had a spontaneous decrease in portal pressure.
In summary, there is some evidence suggesting that AVT may decrease portal pressure immediately after antiviral interferon-based therapy. There are no data regarding the long-term effect of AVT in portal pressure. However, it seems that the effect might not be maintained in the long term, as suggested by the fact that a third haemodynamic measurement performed in six non-sustained viral responders patients 1 year after stopping treatment, showed a significant increase in HVPG.21 Further studies are needed to determine whether the early portal pressure-reducing effect of AVT is maintained in the long term, especially in sustained viral responders.

Is the magnitude of change in portal pressure after antiviral therapy relevant?

Several reports12,13 have clearly suggested that the achievement of an adequate portal pressure reduction after pharmacological treatment of PHT decreases the probability of developing severe manifestations of end-stage liver cirrhosis such as variceal bleeding, spontaneous bacterial peritonitis, hepatorenal syndrome and even death. This threshold reduction of portal pressure has been estimated as an absolute reduction of HVPG values below 12 mm Hg or as a decrease by more than 20% of baseline value after treatment, and therefore, this adequate response is considered as the goal of treatment of PHT.

The magnitude of the decrease in HVPG after AVT has been only assessed in one study,21 in which 80% of patients with severe PHT at baseline, as defined by an HVPG value greater than 12 mm Hg, had a clinically relevant decrease in portal pressure at the end of treatment (Figure 4). Therefore, it is possible to speculate that if the portal pressure decreasing effects of AVT were maintained in the long term, AVT could provide an effective prevention of complications of PHT. However, it is very important to emphasize that the effects of AVT on portal pressure have been assessed only in a very small number of compensated cirrhotic patients and that no clinical end-points have been assessed. Therefore, there is not enough evidence to recommend the use of antiviral treatment in the management of clinical events related to PHT. In a different setting, the recent study by Groszmann et al.25 has shown that non-selective beta-blockers are ineffective in preventing varices in unselected compensated patients with cirrhosis and PHT (minimal HVPG of 6 mm Hg). Two hundred and thirteen such patients were randomly assigned to receive timolol, a non-selective beta-blocker (108 patients), or placebo (105 patients). The primary end-point was the development of gastro-oesophageal varices or variceal haemorrhage. Endoscopy and HVPG measurements were repeated yearly. During a median follow-up of 54.9 months, the rate of the primary end-point did not differ significantly between the timolol group and the placebo group (39% and 40%, respectively; P = 0.89), nor were there significant differences in the rates of ascites, encephalopathy, liver transplantation, or death. As expected, varices developed less frequently among those patients in whom the HVPG decreased by more than 10% at 1 year and more frequently among those in whom the HVPG increased by more than 10% at 1 year.

In summary, further studies are needed to evaluate whether long-term use of AVT may delay the appearance and decrease the severity of manifestations of PHT.

Is the effect of antiviral therapy on portal pressure translated to clinically relevant variables?

The description of the probable effect of AVT on portal pressure is a very important finding from a pathophysiological point of view; however, there are limited data regarding the effects of AVT on clinical manifestations of PHT. A recent randomized study (COPILOT study) was performed in a relatively large number of previous non-responders to AVT in HCV-infected compensated cirrhotic patients with either continuous pegylated interferon-alpha 2b (1.5 μg.kg/week) and colchicine (0.6 mg twice daily) as a potentially antifibrogenic drug.23 Patients underwent an extensive follow-up including clinical assessment, and repeat liver biopsies, ultrasonographic and endoscopic examinations, as well as clinical outcomes were evaluated. Interestingly, the number of patients who had variceal haemorrhage during follow-up was lower in the interferon group [11 of 42 (26%) in the colchicine-treated group versus 1 of 26 (4%) in the interferon group]. In addition, the cumulative probability of being free of clinical manifestations of PHT was significantly greater in the interferon-treated patients. This study suggests that irrespective of
its antiviral effect, continuous AVT could have a potential role in the prevention of complications of PHT. Unfortunately, the design of this large study does not include haemodynamic measurements that could provide relevant information regarding pathophysiological aspects. Again, these results are clearly preliminary and should be confirmed by this mentioned study and other ongoing large-scale trials.

Future investigations

The existence of a possible effect of AVT on portal pressure and also in the clinical manifestations of PHT is an exciting field that should be extensively studied in the coming years. First, it is crucial to evaluate whether cirrhotic patients who undergo sustained viral response also have a sustained reduction in portal pressure, and also whether the magnitude of this effect is relevant in terms of haemodynamic response and clinical end-points such as variceal bleeding, development of ascites and survival.

Another important issue to consider is the design of possible strategies of long-term interferon-based therapies aimed not at virological end-points but at variables related to clinical manifestations of PHT. Duration, dosage, adverse events and costs of this therapeutic approach are critical. It is important to emphasize that an adequate monitoring of these therapies should include the evaluation of changes in portal pressure. Taking into account that liver biopsy is subject to several limitations (different histopathological classifications; significant intra/interobserver variability in the interpretation of liver samples; and heterogeneous distribution of fibrosis throughout the liver), it has been recently suggested that HVPG measurements may be even more precise than histological evaluation in order to determine the severity of hepatic damage.24

On the other hand, haemodynamic measurements are easy and highly reproducible, and liver biopsy during the procedure is possible. Moreover, HVPG represents overall architectural changes and vascular distortion of a greater volume of liver parenchyma, allowing a more thorough estimation of liver damage. Treatment of decompensated cirrhotic patients is another interesting field, mainly in those who are waiting for liver transplantation, as reinfestation of the allograft with hepatitis C virus markedly affects their likelihood of survival. Some promising studies evaluating the safety and efficacy of AVT under a low accelerating dose regimen in cirrhotic patients awaiting liver transplantation have been recently published.25–28 Although all these studies comprised a relatively low number of patients under different therapeutic approaches, a significant proportion of those patients who underwent virological response during the treatment remained free of infection after liver transplantation, ranging from 25% to 80%. Therefore, it has been suggested that patients with a MELD score (the parameter currently used by most liver transplant groups and organizations for graft allocation) of 18 or less might receive AVT while on the waiting list.29 However, the possibility of expanding AVT to patients with decompensated liver disease should be still cautiously and extensively evaluated.

The mechanisms implicated in portal pressure decreasing effects should be also elucidated. Taking into account that the reduction in HVPG seems to be greater in those patients with virological response, the decrease in liver inflammation associated with antiviral activity may be the primary mechanism implicated in the improvement of PHT after AVT. However, in vitro studies have suggested that interferon-alpha has antifibrotic properties,30 as well as a suppressive effect on proteins (like tissue growth factor beta) that are involved in the process that leads to an activated phenotype of hepatic stellate cells, characterized by increased proliferative, motile and contractile properties in these cells.31 As stellate cell activation represents an essential step towards the development of both liver fibrosis and PHT, one may speculate that interferon-alpha might act as an antifibrotic and anti-inflammatory cytokine besides its proven antiviral activity, and that its beneficial effects may not be limited to inhibition of viral replication. However, current AVTs are not effective in eliminating the viral infection in a significant population of patients. Therefore, the HCV epidemic has triggered intensive research efforts towards the development of more effective drugs. Hepatitis C virus is a small, enveloped virus that contains a single-stranded RNA genome encoding a polyprotein of at least 3000 amino acids.32 The polyprotein is a precursor of several structural and non-structural proteins. The structural proteins are released via proteolysis by host signal peptidases, whereas the two viral proteases, NS2 and NS3/NS4a, are responsible for the non-structural polyprotein processing. The NS3/NS4a serine protease mediates proteolysis at the NS3/NS4a, NS4a/NS4b, NS4b/NS5a and NS5a/NS5b junctions,33,34 playing a key role in HCV polyprotein processing and, therefore, viral replication. Given its essential role in the process of HCV replication, the viral NS3/4a serine protease is the most intensively pursued anti-HCV target for drug development. Potent inhibitors of this viral protease such as BILN 2061 and VX-950 are currently in the clinical development phase. Interestingly, in two subsequent placebo-controlled studies of similar design,35 200 mg BILN 2061 twice daily was administered for 2 days to 10 patients with advanced liver fibrosis and to 10 patients with compensated cirrhosis, all of them genotype 1. Transient viral RNA reductions of 2–3 log10 copies/mL were achieved in most of the patients, and virological responses were similar in interferon-alpha non-responder and treatment-naive patients, as well as in patients with high and low baseline viral RNA concentrations. Whether protease inhibitors will be able to improve the degree of PHT via their potent antiviral effect in patients with HCV-related cirrhosis has yet to be elucidated. Clearly, further studies are required.

On the other hand, chronic infection with hepatitis B virus remains an important cause of liver cirrhosis and hepatocellular carcinoma.36,37 Although there is no direct evidence of a possible beneficial effect of AVT in PHT syndrome in these patients, both lamivudine and peginterferon have consistently shown their capacity to improve necroinflammatory activity and fibrosis in this setting. Histological data from several trials have revealed significant reductions in necroinflammatory activity and delayed progression of fibrosis after 1 year of lamivudine compared with placebo.38–40 Furthermore, a meta-analysis of data from three trials showed that 1 year of lamivudine treatment was also associated with a significant reduction in progression to cirrhosis compared with placebo.41 In an interesting study aimed to assess the histological outcome of long-term lamivudine treatment in patients with chronic hepatitis B, 35/63 (56%) patients showed ≥2 points improvement in necroinflammatory activity after 3 years of therapy. Moreover, fibrosis improved ≥1 level in 20/30 (66%) patients with advanced liver fibrosis or cirrhosis.42 Interferon-alpha has been also extensively used for the treatment of chronic HBV infection. In a recent study comparing the efficacy of a 48 week cycle of treatment with either peginterferon-alpha 2a or lamivudine, both groups showed a similar rate of histological
response (49% versus 51%, NS), defined as a reduction of at least two points in the histological activity index score 24 weeks after stopping the therapy.33 This index scored both inflammation and fibrosis, together. Finally, patients with decompensated HBV-related cirrhosis chronically treated with lamivudine have a distinct biphasic survival pattern, with an ~10-fold reduction in the annualized patient death rate after the first 6 months of therapy.11 The actuarial 3 year survival of all patients and those who lived ≥6 months was 73% and 88%, respectively. This high rate of patient survival is significantly greater than the 40% reported in uncontrolled patients with decompensated HBV-related cirrhosis.35,44 In summary, these data provide a rational basis to speculate about a possible impact of AVT in the PHT syndrome in patients with HBV-related cirrhosis. Further studies are necessary once again.

Transparency declarations
None to declare.

References


