

OCCASIONAL VIEWPOINT

Assessment of therapeutic benefit of antiviral therapy in chronic hepatitis C: is hepatic venous pressure gradient a better end point?

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Chronic hepatitis C is a major healthcare problem. The response to antiviral therapy for patients with chronic hepatitis C has previously been defined biochemically and by PCR. However, changes in the hepatic venous pressure gradient (HVPG) may be considered as an adjunctive end point for the therapeutic evaluation of antiviral therapy in chronic hepatitis C. It is a validated technique which is safe, well tolerated, well established, and reproducible. Serial HVPG measurements may be the best way to evaluate response to therapy in chronic hepatitis C.

improvement in hepatic histology to those patients with biochemical response. There are also other data to support the finding that the histological response may be partly independent of biochemical and virological effects of interferon monotherapy, and that continuing treatment for long periods in biochemical non-responders may improve both grading and staging of liver histology. This could be related to the antifibrogenic and anti-inflammatory effect of interferon.^{7 8 10–16}

“The relationship between virological response to therapy as a surrogate marker for the arrest or delay in the progression to cirrhosis has not been clearly established”

Chronic hepatitis C is a major healthcare problem: there are some 170 million chronic hepatitis C virus (HCV) carriers throughout the world of whom an estimated four million are in the USA and five million in Western Europe.¹

HCV accounts for 20% of cases of acute hepatitis, 70% of cases of chronic hepatitis, 40% of cases of end stage cirrhosis, 60% of cases of hepatocellular carcinoma, and 30% of cases of liver transplantation. In patients with chronic hepatitis C, one of the first findings that signal the development of cirrhosis is a decrease in platelet count, indicative of portal hypertension and hypersplenism. About 20% of patients with chronic hepatitis C develop cirrhosis in 10–20 years, and may die from liver related causes.^{2 3} Antiviral therapy is used to try and prevent this progression.

The response to antiviral therapy for patients with chronic hepatitis C was at first only defined biochemically as a reduction in an elevated serum alanine aminotransferase level. However, today, detection of HCV RNA by polymerase chain reaction (PCR) is the “gold standard” to monitor treatment in HCV patients.^{4 5}

However, the relationship between virological response to therapy as a surrogate marker for the arrest or delay in the progression to cirrhosis has not been clearly established. Studies have shown that a sustained biochemical or virological response is associated with a significant decrease in inflammation and more importantly in fibrosis.^{6–9} Furthermore, Shiffman and colleagues¹⁰ showed that one third of patients who had no biochemical response after interferon therapy achieved similar

However, there are several important limitations and sources of bias which prevent an accurate and reliable evaluation of the histological benefit of antiviral therapy for chronic hepatitis C. There are inconsistencies in the definition of pathological features, processing of specimens, sampling errors, and intra/interobserver variability, so that changes in liver histology are not precise quantitative estimates.¹⁷ Flamm and colleagues¹⁸ demonstrated histopathological heterogeneity in chronic HCV infection: 34% of patients had a different fibrosis score in each biopsy sample. Moreover, there is no firm evidence that fibrosis is regularly distributed throughout all of the liver,^{19 20} thus the usual right sided biopsy may not be representative of “true” fibrosis.

Although changes in histological fibrosis can be considered the closest to “the true end points” of liver related morbidity and mortality, obtaining reliable information from biopsies may be difficult and therefore it will be of fundamental importance to look for additional parameters that can be measured more quantitatively and accurately.

Measurement of portal pressure^{21–23} may represent this important parameter. Portal hypertension is the most common and lethal complication of chronic and progressive liver disease. Variceal haemorrhage, ascites, systolic blood pressure, and even portal-systemic encephalopathy are part of this syndrome and prognosis is

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Abbreviations: HCV, hepatitis C virus; PCR, polymerase chain reaction; HVPG, hepatic venous pressure gradient; WHVP, wedge hepatic venous pressure

directly related to portal pressure elevation. Portal pressure has been shown by several studies to be an independent prognostic variable in cirrhotic patients who have not bled from varices and also in those who have bled.²⁴

“Portal hypertension is the most common and lethal complication of chronic and progressive liver disease”

Once a patient develops portal hypertension this becomes the pacemaker marking the progression of liver disease.

Portal pressure is usually measured indirectly by evaluating wedged or occluded hepatic venous pressure.^{22–23} This is a well established technique that consists of introduction of a catheter into the right hepatic vein after which the catheter is advanced until it is “wedged” or a balloon is inflated.^{24–26} The occluded area is quite large and larger than the area with the catheter wedged, and therefore the pressure obtained is the average pressure of many hepatic sinusoids; this reduces the possibility of sampling error due to heterogeneity in the progression of fibrosis in different areas of the liver. The area of the liver that is investigated with this method is much larger than the comparatively minute area analysed by liver biopsy. The occluded or wedged pressure is corrected by subtracting the free hepatic venous pressure or the pressure of the inferior vena cava, the result being the hepatic venous pressure gradient (HVPG).

Thus changes in HVPG can be considered as an adjunctive end point for the therapeutic evaluation of antiviral therapy for chronic hepatitis C.^{21–23 27 28} This is because it is a validated technique which is safe, well tolerated, well established, and reproducible, there is a small standard error,²⁴ and it is known to be a prognostic factor for long term survival in cirrhosis.²⁴

In all of our centres we use the balloon catheter method which makes the technique easier to use and less subject to technical errors.²⁶ Its value as a prognostic marker in cirrhosis, especially of alcoholic aetiology,²⁹ has recently been reviewed and established by many groups.²⁴ There are also studies reporting its use in chronic viral hepatitis although these are fewer in number.^{21–23 30 31} In the most recent study in cirrhotic patients with chronic viral hepatitis C, measurements of wedge hepatic venous pressure (WHVP) accurately reflected portal pressure in both alcoholics (90%) and HCV related liver disease (94%)²² (that is, WHVP is as accurate a measure of portal pressure in alcoholic cirrhosis^{24 29} as in HCV related cirrhosis). Moreover, the correlation with portal pressure was as good in asymptomatic patients as in those with decompensated cirrhosis.²²

“HVPG is a dynamic test that can adequately reflect progression of disease in the precirrhotic stage”

It is established that the gradient between wedged and free hepatic pressure, as an expression of intrahepatic resistance, does not exceed 5 mm Hg in the absence of significant liver disease, whereas a gradient of more than 5 mm Hg is always associated with significant changes on liver biopsy.^{30 31} HVPG is a dynamic test that can adequately reflect progression of disease in the precirrhotic stage. Pichiotti and colleagues²³ found that there is an association between the severity of the piecemeal necrosis and sinusoidal pressure. In one of our centres, Van Leeuwen *et al* found that WHVP increased with histological progression of chronic hepatitis, and that portal hypertension was present before histologically detectable cirrhosis developed (the increase in HVPG reflecting an increase in intrahepatic vascular resistance).³⁰

“Serial HVPG measurements may be the best way to evaluate response to therapy in chronic hepatitis C”

Thus serial HVPG measurements may be the best way to evaluate response to therapy in chronic hepatitis C, particu-

larly in later stages (III and IV) when fibrous deposition is significant. Two studies have reported results of HVPG measurements in patients with chronic hepatitis C before and after treatment with interferon.

Garcia-Tsao and colleagues,²⁷ in a preliminary double blind placebo controlled trial, evaluated the effect of interferon on HVPG in patients with chronic hepatitis C and portal hypertension. The percentage change in HVPG was significantly greater in the interferon treated group compared with the placebo group ($p < 0.01$). However, there was no correlation between the decrease in HVPG and decrease in alanine aminotransferase, and there were no data on PCR HCV-RNA. In another paper, Valla and colleagues,²⁸ evaluating 39 hepatitis C cirrhosis patients treated with interferon for 48 weeks, measured HVPG in five and found a decrease in mean HVPG from 13.8 (3.9) to 11.1 (3.6) mm Hg, while in five control patients it increased from 13.2 (4.8) to 14.6 (2.6) mm Hg without a parallel histological improvement. Although these changes were not statistically significant, there was a trend towards a reduction in HVPG in the treated group with a 20% reduction in baseline HVPG. Those observations, if confirmed, suggest that this could reflect the “antifibrotic” and consequent secondary haemodynamic effect of interferon, rather than an antiviral effect. Clearly this effect can only be evaluated using HVPG measurements.

A further advantage of measuring HVPG is that it can be performed together with a transjugular liver biopsy^{24 25 32 33} which would give concomitant histological information. The risks related to the procedure are no higher than the percutaneous route in patients of similar risk for biopsy and it is safer in high risk patients such as cirrhotics with small livers, or moderate ascites, haemodialysed patients, or haemophiliacs. With the newer needles, adequate liver samples are obtained even when the liver is cirrhotic. The technical success rate in our centres is more than 95%, and the specimen obtained is adequate for histology in 90% of cases.³³ In precirrhotic patients, one would reasonably expect the proportion of adequate samples to be higher.

CONCLUSION

Because there is little variability in the measurement of HVPG, a numerical progression represents true worsening of the disease process, and if there is cirrhosis it also provides reliable prognostic information for survival.^{29 34} Thus measurement of HVPG could be considered as a dynamic marker of disease progression in patients with HCV and an end point in antiviral therapy, irrespective of antiviral response. The optimal first groups to study would be those with fibrosis in the pretreatment biopsy as well as compensated cirrhotics who are given antiviral therapy. Further studies should assess the best timing of this measurement, and verify its prognostic utility in monitoring response to antiviral therapy compared with the current “surrogate” markers as well as new ones such as serum markers of fibrosis.

“Measurement of HVPG could be considered as a dynamic marker of disease progression in patients with HCV and an end point in antiviral therapy, irrespective of antiviral response”

In the future it is likely that a panel of fibrosis markers will be used, reflecting both collagen deposition and breakdown. These in themselves will need to be correlated with portal pressure elevation as well as suitable histological material stained for collagen. Portal pressure measurement will be the important link prognostically between histology and serum markers of fibrosis.

In order to test this, therapeutic trials should evaluate HVPG combined with transjugular liver biopsy before and

after treatment. This combined procedure is easy to perform in practice.³² In patients who develop HVPG >10 mm Hg, complications of portal hypertension are known to develop²⁴⁻³⁴ and this could be an end point in studies. In patients with normal HVPG, maintaining a normal pressure should be a sign of good prognosis. In virological non-responders it is not known whether a liver biopsy after treatment is appropriate to evaluate therapeutic benefit following antiviral therapy, and in cirrhotics it is not clear what should be measured to assess long term response. In these two groups, measurement of HVPG could be particularly useful. Thus HVPG could be a universally applied measurement of progression with and without antiviral therapy, irrespective of virological response in patients with chronic hepatitis C.

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