Editorial

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Direct acting antivirals for decompensated cirrhosis. Efficacy and safety are now established

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Chronic liver injury of any etiology most commonly results in liver fibrosis and eventually cirrhosis and portal hypertension with the attendant risks of decompensated liver failure, hepatocellular carcinoma (HCC) and death. Several studies have shown that successful treatment or removal of the underlying liver injury can result in regression of liver fibrosis and cirrhosis in some patients [1]. Reversal of liver cirrhosis was observed in 49% of patients with compensated hepatitis C virus (HCV) cirrhosis treated with interferon (IFN) based therapy. Sustained virological response (SVR) was the only independent predictor of reversal [2]. Eradication of HCV infection with IFN based therapy also reduces the risk of liver failure, HCC, liver-related mortality, all cause mortality and the need for liver transplantation (LT) in those patients with compensated liver cirrhosis [3,4].

The improved SVR rates and safety profiles of all oral direct acting antivirals (DAA) has led to the treatment of some patients who would not have received widespread treatment in the IFN era. One such group is the decompensated cirrhotic patients, who have a poor prognosis, have limited treatment options and make up a large proportion of those awaiting LT [5]. Several open label clinical trials of DAA in decompensated HCV patients have recently demonstrated SVR rates above 80% and improvements have been observed in the Child-Pugh-Turcotte (CPT) and/or model for end-stage liver disease (MELD) scores in a significant proportion of patients after relatively short follow up [6–9]. These improvements are largely attributable to changes in biochemical parameters of serum bilirubin and albumin. The results for SVR observed in these studies are indeed impressive given that the majority of these patients had several characteristics that would predict poor response. However, there are some limitations to the studies that make it hard to draw definitive conclusions about benefits other than viral eradication. The absence of comparator control groups makes it difficult to determine if viral eradication and improvement in MELD and CPT scores result in improved survival. The effects of viral eradication on the clinical aspects of hepatic decompensation are not well represented in these studies; and the high SVR rates achieved in these open label studies would likely now hamper enrolment in any future placebo control trials designed to answer these questions. We are therefore left wondering whether viral eradication results in a reduction in morbidity and mortality, improves transplant free survival and if DAA are indeed safe in this patient population. Given that LT is the only available treatment for decompensated cirrhosis and that there is a growing disparity between donor organ availability and the number of patients wait-listed for LT, we need to determine which population of patients should receive DAA and if treatment can improve liver function so that these patients have improved transplant free survival.

In a study published in this issue, Foster and colleagues have addressed some of the shortfalls of these open label studies using the early access program (EAP) for treatment in the HCV Research UK registry. Patients were treated with combination DAA for 12 weeks at the discretion of the investigator. The study cohort was prospectively enrolled from registry patients while the control cohort was retrospectively enrolled from the same registry prior to the availability of DAA EAP [10]. Primary outcome was SVR at 12 weeks and secondary outcomes were changes in MELD score, and development of adverse outcomes such as decompensation, HCC, sepsis, LT, death and hospitalization observed over the 12 week treatment period and 12 weeks of follow-up.

Similar to what was seen in the open label studies, SVR was achieved in over 80% of patients with severe HCV related liver disease and was more frequently observed in genotype 1 patients and in genotype 3 patients who received the pan-genotypic NS5A inhibitor, daclatasvir as part of their treatment regimen. Treated patients had an improvement in MELD score, were less likely to increase MELD score $\geqslant 2$ points, were less likely to have an increase MELD score $\geqslant 2$ points associated with an adverse outcome and were less likely to have a new decompensating event when compared with untreated cohort regardless of SVR outcome. SVR did not predict improvement in MELD score, but patients achieving SVR were less likely to increase MELD score $\geqslant 2$ points and were less likely to have an adverse outcome compared with those who did not achieve SVR. The authors identified baseline MELD score and albumin as predictors of adverse outcomes. Additionally, the authors attempted to use baseline characteristics to create a model that would predict benefit. Patients older than 65 years with reduced hepatic synthetic function

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(serum albumin ⩽35 g/L) were less likely to derive a benefit from therapy, however this model does not discriminate well enough (AUROC of 0.5484) to determine if patients should be treated or if treatment should be deferred in favor of LT.

The study showed no difference in incidence of HCC, sepsis, or death between treated and untreated patients over the 24 week study period. HCC occurred in 6.1% of the treated and 8.0% of the untreated cohort. SVR had no effect on the incidence of HCC, although this is not all that surprising given the 24 week time-frame. The relatively high rate of HCC over this short time period would suggest that some or all of these HCCs were present but not detected on enrolment into the study. It is also unlikely that eradication of HCV would alter the development of HCC within 12 weeks of achieving SVR given that half of the HCC that developed in a large Japanese cohort of patients successfully treated with IFN occurred ⩾37 months after SVR [11]. Studies that have shown a difference in the incidence of HCC between SVR and non-SVR patients have had significantly longer follow up (>6 years) [3].

Importantly from the perspective of safety in treating decompensated patients with DAA, the authors compared the incidence of adverse outcomes between the treated and untreated cohorts and noted that the treatment was generally well tolerated. The study showed no difference in the incidence of hospitalization, sepsis and death between treated and untreated cohorts. This would suggest that these complications are related to the underlying liver disease and not related to the treatment regimen. The baseline median MELD score was 11 in both treated and untreated cohorts but some patients had MELD scores of up to 32. Almost 10% of the treated cohort were classified as CPT class C and over 40% had ascites indicating a significant degree of advanced liver disease that is unlikely to improve over the short term after eradication of HCV. It is likely that some of these patients with decompensated cirrhosis had reached a point where antiviral therapy was less effective in improving liver function. In the Ally-1 study of sofosbuvir/daclatasvir and ribavirin, Poordad and colleagues observed that CPT class C patients had lower SVR (56%) than CPT class A (92%) and B (94%) patients [8]. In the Solar 2 study of sofosbuvir/ledipasvir and ribavirin, the most common reason for non-SVR in the CPT class C patients was death from progressive liver failure [9]. This "point of no return" has also been illustrated in the past with the treatment of decompensated hepatitis B virus (HBV) cirrhosis. Nucleoside analogue treatment of decompensated HBV cirrhosis is associated with a reduction in all cause mortality when compared with control (RR = 0/5, 85% CI 0.3–0.8) [12]. In a study of 70 patients with decompensated HBV cirrhosis treated with entecavir, the cumulative incidence of mortality or LT was 17% at 2 years for the whole group but 36% for CPT class C patients, despite viral suppression in 92% of patients and improvements in CPT and MELD scores [13].

We have now seen multiple reports that DAA are highly efficacious in a population of patients in most need of viral eradication. Viral eradication results in improvements in MELD and CPT scores denoting improvement in liver function in studies of short term follow up. It appears that these regimens are relatively safe, with most adverse events caused by the underlying disease process. However, there is a proportion of patients that do not seem to gain immediate benefit from DAA therapy. Whether these patients are slower to improve or will remain with decompensated liver disease and at risk of further complication requires longer follow up studies. Additionally, it will take time and further study to see if these patients have been disadvantaged in the prioritization system for organ allocation. Lastly we need the results of ongoing studies of portal pressure measurements (NCT01687257) and long-term registries (NCT02292706) to identify those patients less likely to benefit from DAA therapy.

Conflict of interest

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References

[1] Serpaggi J et al. Direct and indirect evidence for the reversibility of cirrhosis. Hum Pathol 2006;37:1519–1526.

[2] Poynard T et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology 2002;122:1303–1313.

[3] van der Meer AJ et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012;308:2584–2593.

[4] Morgan TR et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology 2010;52:833–844.

[5] Kim WR et al. OPTN/SRTR 2013 Annual Data Report: liver. Am J Transplant 2015;15:1–28.

[6] Charlton M et al. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. Gastroenterology 2015;149:649–659.

[7] Curry MP et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med 2015;373:2618–2628.

[8] Poordad F et al. Daclatasvir with sofosbuvir and ribavirin for HCV infection with advanced cirrhosis or post-liver transplant recurrence. Hepatology 2016. http://dx.doi.org/10.1002/hep.28446, [Epub ahead of print].

[9] Manns M et al. Ledipasvir/Sofosbuvir with Ribavirin is safe and efficacious in decomensated and post-liver transplatation patients with HCV infection: preliminary results of the SOLAR-2 trial. J Hepatol 2015;62:S187–S188.

[10] Foster GR et al. Cohort study of the impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol 2016;64:1224–1231.

[11] Nagaoki Y et al. Development of hepatocellular carcinoma in patients with hepatitis C virus infection who achieved sustained virological response following interferon therapy: a large-scale, long-term cohort study. J Gastroenterol Hepatol 2015. http://dx.doi.org/10.1111/jgh.13236, [Epub ahead of print].

[12] Lok AS et al. Antiviral therapy for chronic hepatitis B viral infection in adults: a systematic review and meta-analysis. Hepatology 2016;63:284–306.

[13] Shim JH et al. Efficacy of entecavir in treatment-naive patients with hepatitis B virus-related decompensated cirrhosis. J Hepatol 2010;52:176–182.