

## Hepatology highlights

Magnus McLeod, Arman Khorasani-Zadeh, Kevork M. Peltekian

Division of Digestive Care and Endoscopy, Queen Elizabeth II Health Sciences Centre and Dalhousie University, Halifax, Nova Scotia, Canada.

### Boceprevir and telaprevir for chronic genotype 1 hepatitis C virus infection: a systematic review and meta-analysis

**Manzano-Robleda MC, et al.** This article should appeal to health insurance payers and policy makers who are in the business of management of hepatitis C infection, especially within health care systems that will not have access immediately to the newer direct-acting antiviral agents which were reviewed recently in the Annals of Hepatology.<sup>1</sup> In this meta-analysis, data were extracted systematically allowing guidance regarding efficacy of treating chronic hepatitis C infection using first generation protease inhibitors (PI): boceprevir and telaprevir, no matter if patients were previously exposed to pegylated interferon plus ribavirin (PR). The results of this study may also assist clinicians the usage of old drugs with better outcomes especially when individualized treatments of hepatitis C genotype 1 are considered. The goal of this systematic analysis was to summarize the world literature for predictors of the primary outcome for sustained viral response (SVR) defined as negative viral load at week 12 or 24.

After analysis of 33 studies (10,525 patients) with a meta-regression, previously treated patients exhibited greater benefit from PI + PR (RR, 3.47) but minimal adverse events (RR, 1.01) and low discontinuation rate (RR, 1.69).

Furthermore, if there was any doubt about it, the study confirmed that PR-treated patients have a very low probability of achieving an SVR with a new round of PR treatment (17%), whereas treatment-naïve patients receiving PR achieved only 41% SVR. Predictors of greater SVR included IL-28 genotype TT, non-black race, low viral load, younger age, absence of cirrhosis, statin use, undetectable viral load at the first anemia episode or at week 2 of treatment, and low IL-6 levels. This type of analysis allows the identification of potential factors that may be utilized for individualized treatment of patients with better outcomes. Unfortunately, in the absence of the primary datasets from all 33 studies, more specific conclusions cannot be made regarding independent predictors of SVR. Practically, most of us have been using undetectable viral load at week-2 as a predictor of SVR especially when IL-28 genotyping is not available.

The authors are right! The newer direct-acting antiviral agents will take over chronic hepatitis C infection treatment but not until payers and policy makers appreciate the advantages of direct-acting antiviral agents in spite their expense tags. Most clinicians who have been treating hepatitis C for the last two decades have moved on and will be unlikely use PI + PR as an alternative.

### Factors associated with recurrence and survival in liver transplant patients with hepatocellular carcinoma: a single center retrospective study

**Hoyos S, et al.** In this issue of the *Annals of Hepatology*, the liver transplantation team from

Medellin, Colombia, shares their experience on the advanced management of hepatocellular carcinoma. Often these self-reflective studies are repetitive but necessary. Hepatocellular carcinoma is one of the deadliest tumors worldwide; there is a need to ensure it behaves the same way in different continents especially if we plan to tackle this scourge globally – in our opinion, the global approach is the only way we can conquer hepatocellular carcinoma!

The liver transplantation population is this center includes only 16.4% with hepatocellular carcinoma; while the cirrhosis etiologies requiring transplantation is equally distributed between alco-

Correspondence and reprint request: Dr. K. M. Peltekian.  
Queen Elizabeth II Health Sciences Centre,  
1276 South Park Street, Victoria General Site Room 9-915,  
Halifax, N.S., Canada B3H 2Y9,  
Tel.: 19024737833, Fax: 19024732783  
E-mail: kevork.peltekian@dal.ca

hol in 22.2%, followed by hepatitis B virus infection in 20.4%, and hepatitis C virus infection in 18.5%. Similar to other studies, hepatocellular carcinoma recurred in 7.4% patients after a mean 81 months. During mean follow-up of 67.9 months, 25.9% of these patients died. Recurrence and survival of patients with liver transplantation for hepatocellular carcinoma in this study had a similar behavior as that reported in the world literature. The factors as-

sociated with recurrence and mortality included vascular invasion, poorly differentiated tumor, and local satellite metastasis.

The authors should be congratulated for this study appreciating the small number of patients studied, the extended length of study period, and often the complexity in accessing information regarding medical services in Colombia.

#### The performance of prognostic models as predictors of mortality in patients with acute decompensation of cirrhosis

**Fayad L, *et al.*** These authors from Santa Catarina, Brazil, performed an elegant study comparing different Model for End-Stage Liver Disease (MELD) scoring models at admission and 48 hours post admission to prognosticate outcomes in patients with decompensated cirrhosis. The original MELD score incorporates bilirubin, creatinine and INR into a formula providing a continuous variable that is a very accurate predictor of 90-day mortality in patients with cirrhosis.<sup>2</sup> The MELD score was adopted in 2002 by UNOS for prioritizing allocation of organs for liver transplantation since it predicted 3-month mortality in cirrhotic patients on the pre transplant waiting list.<sup>3</sup>

In this study, data from 123 patients were analyzed. These patients had a mean MELD score of  $16.43 \pm 7.08$ . Twenty-seven (22%) of patients died during their current hospitalization. The various MELD models utilized in this study including MELD-Na, MESO, iMELD, Refit-MELD and Refit MELD-Na, all had similar area-under-the curve regression for predicting mortality both when these models were calculated on admission (p-value > 0.05) and after 48-hours following hospitalization (p-value > 0.05). Interestingly, when models were calculated based on patient data available after

48-hours of hospitalization, there was significantly better correlation with outcomes compared to MELD scores calculated at admission (p-value < 0.05), but not for MELD-Na and iMELD.

This information gives the readers a better appreciation for the use of MELD scoring systems in the hepatology practice together with a better understanding of the change in MELD score in prognosticating outcomes of patients while in hospital. The MELD score on its own is a snapshot of liver function which could be affected by variables that do not correlate with decreased liver function such as a rising creatinine in the setting of over-diuresis or prolonged INR due to use of antibiotics and malnutrition. Intuitively, MELD changes therefore may be transient and reversible. In view of these considerations, the result of this study by Fayad, *et al.*, lead one to strongly consider the change in MELD as being an optimal prognostication tool that could be used in multiple settings. This could lead to improved use of therapeutics as well as improved information in regards to discussing prognosis with patients and families during hospitalization. Further research is needed, but this change in MELD score may prove useful in several settings of which include liver transplantation allocation, treatment for alcoholic hepatitis and even potentially prognosticating outcomes in hyperacute, acute or subacute liver failure.

#### Factors associated with 25-hydroxyvitamin D levels in patients with liver cirrhosis

**Costa Silva M, *et al.*** In this issue the authors describe their current research investigating the associations of vitamin D and cirrhosis. This is a topic of interest in other medical fields as vitamin D deficiency has been linked to increased risk of cancer and autoimmune disease.<sup>4,5</sup> Vitamin D deficiency is

associated with cirrhosis and has been associated with higher mortality<sup>6</sup> but the pathophysiology of this association has not been completely elucidated. Costa Silva M. *et al.* shed more light on vitamin D deficiency and its impact on patients with cirrhosis using a more stringent methodology, appropriate healthy control and patients with continuum of advanced liver disease rather than limiting it to only those with very advanced liver disease.

The authors made interesting observations in this cross-sectional study of 133 cirrhotic patients. The mean 25-hydroxyvitamin D [25(OH)D] levels were  $27.03 \pm 6.22$  ng/mL in cirrhotic patients compared to controls who had a mean level of  $32.34 \pm 11.38$  ng/mL ( $p = 0.018$ ). Interestingly, only 14.3% of cirrhotic patients had levels below 20 ng/mL. The prevalence of low 25(OH)D was associated with level of adiposity based on higher tricep skin folds as well as non-Caucasian race, but surprisingly not the severity of liver disease. The 25(OH)D levels were also evaluated in the setting of hospitalized patients with decompensated liver disease and although the levels were found to be decreased in hospitalized patients,

there did not seem to be a correlation to severity of liver dysfunction.

In the Discussion section, the authors raise the possible role of 25(OH)D as a negative phase reactant. This finding of 25(OH)D being a negative acute phase reactant could help explain its association in so many disease processes but begs the question of its reliability in accurately measuring vitamin D levels in certain patients such as those with cirrhosis. More research is needed at this point to fully elucidate the role of vitamin D and its implications in liver disease, but, at this point from what is known currently, vitamin D supplementation seems warranted in most patients with liver disease.

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