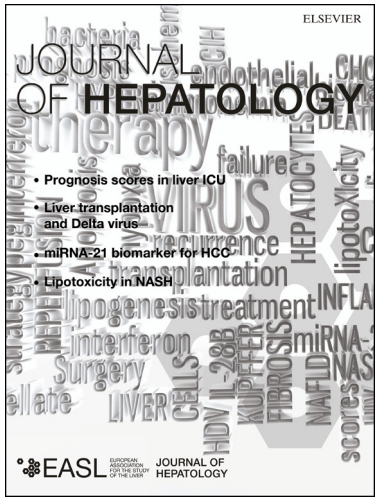


Letter to the Editor

# From the CUPIC study: Great times are not coming (?)

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From the CUPIC study: Great times are not coming (?)

We note, with interest, the findings of the interim results from the CUPIC study reported recently in the Journal of Hepatology[1]. The authors demonstrate a high incidence of serious adverse events (40.0%), and of death and severe complications (severe infection or hepatic decompensation) (6.4%), in a difficult to treat cohort of patients. Most notably however, the authors have proposed that compensated cirrhotic patients with chronic HCV with both thrombycytopaenia (Platelets <100,000) hypoalbuminaemia (<35 g/dL) should not be treated with triple therapy.

There are a number of important considerations for accurate interpretation of the data. Although acknowledged by the authors, it is important to re-emphasise that CUPIC lacked a control group. The author's conclusions must, therefore, be balanced against the published natural history of HCV cirrhotic patients. The benefits of sustained virologic response (SVR) in this group are well documented [2]. Hence, international treatment guidelines generally recommend antiviral therapy in this patient group [3, 4]. Indeed, in controlled trials of dual therapy of patients with decompensated cirrhosis, the treatment group had more favourable outcomes compared to control group [5]. Additionally, treatment of HCV patients on the liver transplant waiting list does not appear to increase overall mortality compared with untreated patients [6]. Thus, the benefits of achieving SVR, in this difficult population, cannot be overstated [7].

CUPIC was not designed or powered for interim safety analysis. Indeed recent data investigating the therapeutic potential of triple therapy in patients with severe fibrosis or cirrhosis demonstrated lower complication rates than those observed in CUPIC[8, 9].

Possible explanations for this difference include multiple treatment centres (n=56) with variation in the treatment and monitoring protocols. In addition 'severe infection' is not clearly defined in the manuscript and this was the most commonly (24 of 32 cases) reported severe complication. Indeed, 7 of the 24 patients who survived a severe infection continued on treatment without requiring a dose reduction and a further unreported number continued treatment at a reduced dose. Deaths in the total cohort were relatively uncommon (n=6, <1%) however neither the albumin level nor platelet count is reported for these. Two of the six deaths reported occurred prior to the introduction of the protease inhibitor which, may indicate that these subjects were poor candidates for treatment.

The association between platelet count and albumin level and mortality during HCV treatment is not novel. Previous work has demonstrated a per annum mortality for HCV patients with thrombocytopaenia alone (defined as platelet count <150,000 rather than the level of 100,000 used in the paper) of 4%, which would correspond to 4 deaths over the course of a year among the 103 thrombocytopaenic patients [10]. Furthermore, hypoalbuminaemia has also been independently associated with increased mortality in cirrhotic patients prompting calls for the adoption of a modified MELD score incorporating albumin[11]. It seems incontrovertible that cirrhotic patients are at greater risk of complication from triple therapy, but suggesting that platelet count (<100,000) and albumin level <35) should preclude consideration for treatment without describing the natural history of untreated HCV in a similar cohort appears unbalanced. For many of these patients, the promise shown in clinical trials of the next generation of directly

acting antivirals, the safety of which in these cohorts remains also untested may well come too late.

Yours etc,

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Diarmaid Houlihan

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