Combination therapy with ACH-3102 and sofosbuvir for 8 weeks achieved rapid sustained viral load declines with 100% SVR12. These results were observed in patients with high baseline viral loads, including 9 patients with a baseline viral load >6 000 000 international units (IU)/mL, 7 of whom had >7 $\log_{10}$ IU/mL. A rapid decline in viral load was also observed after 6 weeks of treatment. The combination treatment was well tolerated with no significant AEs, electrocardiogram findings, or laboratory abnormalities. These observations will inform future clinical trials using ACH-3102 plus ACH-3422 as an interferon- and ribavirin-free regimen for the treatment of chronic HCV infection.

## Prednisolone But Not PTX Improves 28-Day Mortality in Patients With Alcoholic Hepatitis

Written by Maria Vinall

Severe alcoholic hepatitis, defined by a Maddrey's discriminant function (DF) ≥32, has a 28-day mortality rate of about 35%. Clinical trials have shown both corticosteroids and pentoxifylline (PTX) to be of potential therapeutic benefit, and both are recommended in current practice guidelines [Malthurin P et al. *J Hepatol.* 2012; O'Shea RS et al. *Hepatology.* 2010]. However, both are controversial, steroids because of inconsistent trial outcomes and PTX because its use is based on a single trial. Mark Richard Thursz, MD, Imperial College London, London, UK, presented data from the Steroids or Pentoxifylline for Alcoholic Hepatitis trial [STOPAH; ISRCTN88782125], which confirmed a mortality benefit with prednisolone at 28 days. PTX had no impact on disease progression.

STOPAH was a randomized, double-blind, placebo-controlled phase 3 trial designed to assess the efficacy of prednisolone 40 mg daily or PTX 400 mg 3 times daily in the treatment of severe alcoholic hepatitis [Forrest E et al. *Trials.* 2013]. The primary end point was mortality at 28 days. Secondary end points included mortality/transplant at 90 days and 12 months, and diagnostic utility of existing prognostic scores. Other objectives were to assess rates of recidivism and the impact of recidivism on subsequent survival. The study included patients aged ≥18 years with a clinical diagnosis of severe alcoholic hepatitis (ie, DF ≥32), a serum bilirubin >80 µmol/L, and a history of excess alcohol consumption (>80 g/d for men; >60 g/d for women) who had been hospitalized for <4 weeks. Abstinence of >6 weeks prior to randomization, jaundice lasting >3 months, and/or use of either study drug within 6 months were causes for exclusion. Participants were randomized to 1 of 4 groups—placebo/placebo, prednisolone/placebo, placebo/PTX, or prednisolone/PTX—and treated for 4 weeks.

Subjects (n=1092) were mean age 48.7 years (62.7% men; 96% white) with a mean alcohol consumption of 200.1 g/d (149.5 g/day for women). Mean time from admission to treatment was 6.4 days. About 27% exhibited encephalopathy on admission. Laboratory values were similar to those seen in other trials.

The overall mortality rate was 16%. The mortality rate for subjects treated with prednisolone was 13.9% vs 18% for subjects not receiving prednisolone. Mortality among subjects treated with PTX was 16.4% vs 15.5% for those not receiving PTX (Table 1).

The odds ratio for 28-day mortality was 0.72 (95% CI, 0.52 to 1.01; $P=.056$) for prednisolone compared with 1.07 (95% CI, 0.77 to 1.49; $P=.686$) for PTX (Figure 1).

Table 1. Mortality at 28 Days, % (n/N)

| | | Pentoxifylline | | |
|---|---|---|---|---|
| | | No | Yes | Total |
| Prednisolone | No | 16.7 (45/269) | 19.4 (50/258) | 18.0 (95/527) |
| | Yes | 14.3 (38/266) | 13.5 (35/260) | 13.9 (73/526) |
| | Total | 15.5 (83/535) | 16.4 (85/518) | 16.0 (168/1053) |

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Figure 1. 28-Day Mortality

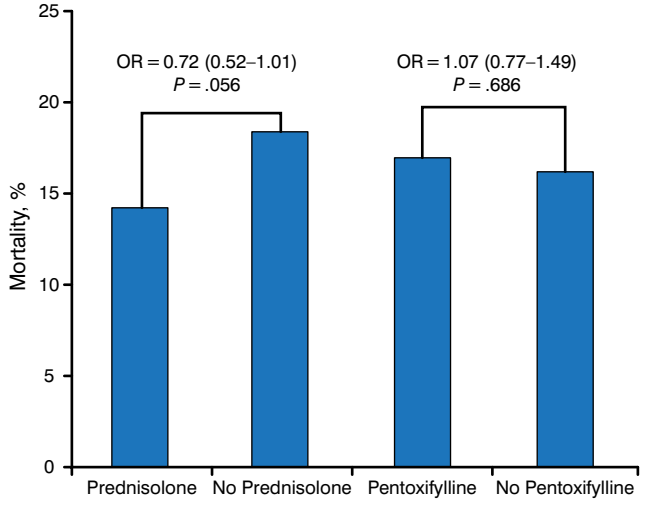


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Table 2. Abstinence and Mortality

| Alcohol Consumption Status (Variable at Day 90) | 1-y Mortality | | | |
|---|---|---|---|---|
| | n | Odds Ratio | 95% CI | *P* Value |
| Not reduced (ie, still drinking as much as or more than when presented) vs abstinent | 478 | 2.99 | 1.47 to 6.05 | < .001 |
| Reduced drinking but higher than safety limits vs abstinent | 478 | 2.28 | 1.07 to 4.86 | .032 |
| Reduced drinking to lower than safety limits vs abstinent | 478 | 2.17 | 1.07 to 4.39 | .031 |

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On multivariate analysis, accounting for disease severity and prognosis, the 28-day odds ratio for mortality in the prednisolone group was 0.609 (95% CI, 0.409 to 0.900; $P = .015$), indicating a potential reduction in mortality of about 40%. Neither treatment had any impact on survival beyond 28 days. Infection, in particular lung infection, was more common in prednisolone-treated subjects.

All 4 prognostic scoring systems (ie, DF, Glasgow Alcoholic Hepatitis Score [GAHS], Model for End Stage Liver Disease [MELD], and the Lille model) were significantly associated with prognosis (all $P < .0001$). However, the area under the receiver operating characteristic curves (AUROC) were relatively low ranging from .69 to .74.

Abstinence is a major determinant of survival after 90 days. Compared with patients who reported complete abstinence, the 90-day odds ratio for mortality for those who reduced their drinking to within government guidelines was double. For those who did not reduce their drinking, it was triple (Table 2).

## DCV/ASV/BCV Improves Sustained Viral Response in Patients With Chronic HCV GT-1 Infection and Compensated Cirrhosis: UNITY-2 Results

Written by Maria Vinall

Andrew J. Muir, MD, MHS, Duke University School of Medicine, Durham, North Carolina, USA, presented data indicating that treatment with an all-oral fixed-dose combination of daclatasvir (DCV)/asunaprevir (ASV)/beclabuvir (BCV; DCV-Trio) with or without the addition of ribavirin (RBV) is associated with high rates of sustained viral response to treatment 12 weeks after therapy (SVR12) in patients with chronic compensated cirrhosis and hepatitis C virus (HCV) genotype 1 (GT-1) infection.

In a phase 2 trial, combination treatment with DCV/ASV/BCV was associated with SVR12 in > 92% of treatment-naïve patients with GT-1 infection and 100% of patients with GT-4 infection [Hassanien T et al. *J Hepatol.* 2014; Everson GT et al. *AASLD* 2013]. UNITY-2 [NCT01973049] was a randomized phase 3 trial that evaluated DCV/ASV/BCV as a fixed-dose regimen with and without RBV in treatment-naïve (n = 112) and treatment-experienced (n = 90) patients with HCV GT-1 infection and compensated cirrhosis. Adults with chronic HCV GT-1a or 1b infection and confirmed compensated Child-Pugh class A cirrhosis with a platelet count > 50 000/mm$^2$, international normalized ratio < 1.7, and albumin > 3.5 g/dL were eligible to participate. Patients were randomized to DCV-Trio (DCV 30 mg/ASV 200 mg/BCV 75 mg) with or without blinded RBV and treated twice daily for 12 weeks. The key efficacy variable was SVR12 (HCV RNA < lower limit of quantification [25 IU/mL] target detected/not-detected) in the treatment- naïve and treatment-experienced patients evaluated separately.

Participants were predominately white (> 80%) men (> 60%) between 58 and 60 years of age. Between 70% and 78% of the participants were GT-1a; less than one-third had the favorable IL28B CC GT polypmorphism; 26% of patients had platelets < 100 000/mm$^2$. Of the 90 treatment-experienced patients, 39% were prior null responders; 9% were partial responders and 18% of patients had relapsed. Nonresponse was characterized as "other" in the remaining 34%.

In the treatment-naïve cohort, 93% of patients receiving DCV-Trio only achieved SVR12 compared with 98% of those who received DCV-Trio plus RBV. Results were similar in the experienced cohort (87% and 93%, respectively; Figure 1) and when analyzed by GT-1 subtype (Figure 2).

No clear difference in SV12 was observed between patients who did and did not receive RBV when assessed by platelet count (< vs ≥ 100 000/mm$^2$), sex, age, baseline HCV RNA, or IL28B GT.

Three patients had on-treatment virologic failure; all were in the treatment-experienced group. Ten patients relapsed (4 treatment-naïve patients; 6 treatment-experienced patients; Table 1). NS5A and NS3 resistance-associated variants (RAVs) did not appear to impact SV12.

Two patients in the DCV-Trio-only group had serious adverse events (AEs) compared with 7 patients receiving