Rapid Sustained HCV Viral Load Reductions Achieved With ACH-3102 Plus SOF

Written by Toni Rizzo

ACH-3102 is a second-generation hepatitis C virus (HCV) nonstructural 5A (NS5A) protein inhibitor with potent activity against HCV genotype (GT)-1 through GT-6 [Zhao et al. EASL. 2012; Yang et al. AASLD. 2011]. ACH-3102 retains activity against multiple HCV variants resistant to first-generation NS5A inhibitors [Nakamoto S et al. *World J Gastroenterol.* 2014; Gao M. *Curr Opin Virol.* 2013; Zhao et al. EASL. 2012; Yang et al. AASLD. 2011]. ACH-3422, an HCV nonstructural 5B (NS5B) uridine nucleotide polymerase inhibitor, is under development for use in combination with ACH-3102.

Edward J. Gane, MD, Auckland Hospital, Auckland, New Zealand, presented interim results of an ongoing phase 2 open-label study of ACH-3102 plus sofosbuvir, which was used as a proxy for ACH-3422. Sofosbuvir is an HCV NS5B uridine nucleotide polymerase inhibitor that has been studied in multiple clinical trials in combination with NS5A inhibitors [Feeney ER and Chung RT. *BMJ.* 2014]. The objective of this study was to evaluate the safety and efficacy of 8 and 6 weeks of ACH-3102 plus sofosbuvir therapy in treatment-naïve patients with chronic HCV GT-1 infection.

Two cohorts of patients were enrolled. In Cohort 1, patients were randomized to receive ACH-3102 plus sofosbuvir for 8 weeks (n = 12) or observation without treatment for 12 weeks (n = 6). Sustained viral response 4 (SVR4) results were obtained before proceeding with Cohort 2. Cohort 2 included the 6 observational patients from Cohort 1 plus 12 newly randomized patients. The 6 Cohort 1 observational patients were assigned to ACH-3102 plus sofosbuvir for 6 weeks. The additional 12 patients were randomized to ACH-3102 plus sofosbuvir for 6 weeks (n = 6) or observation for 10 weeks (n = 6).

The primary end point was SVR at 12 weeks after treatment ended (SVR12) in patients who received 8 or 6 weeks of ACH-3102 plus sofosbuvir. The secondary end points included SVR4, SVR8, rapid virologic response (RVR), end-of-treatment response (ETR), and adverse event (AE) rates.

In Cohort 1, all 12 patients treated with ACH-3102 plus sofosbuvir achieved HCV RNA levels < the lower limit of quantification (LLOQ) by week 3 and < the LLOQ target not detected ($LLOQ_{TND}$) by week 5. Among patients who received 8 weeks of active treatment, 100% achieved ETR, SVR4, SVR8, and SVR12, and 83% achieved RVR. To date, 5 Cohort 2 patients who received active treatment have achieved ETR. Eight patients who completed 4 weeks of treatment have achieved HCV RNA < LLOQ.

Table 1 shows the treatment-emergent AEs occurring in > 10% of Cohort 1 patients.

Table 1. Treatment-Emergent Adverse Events Occurring in > 10% of Cohort 1 Patients Through End of Treatment +4 wk

Adverse Events	Cohort 1 Active (n = 12)	Cohort 1 Observational (n = 6)	All Cohort 1 (n = 18)
Total number of patients, no. (%)	11 (91.7)	4 (66.7)	15 (83.3)
Upper respiratory tract infection, no. (%)[a]	5 (41.2)	2 (33.3)	7 (38.9)
Ligament sprain, no. (%)	2 (16.7)	0	2 (11.1)
Insomnia, no. (%)	2 (16.7)	0	2 (11.1)
Headache, no. (%)	2 (16.7)	0	2 (11.1)

[a]Includes 2 noncoded adverse events (AEs) with a verbatim term of "upper respiratory tract infection" in Cohort 1 observational patients, and 1 AE with a preferred term of "viral upper respiratory tract infection" in Cohort 1 active-treatment patients. Data cutoff: August 19, 2014.

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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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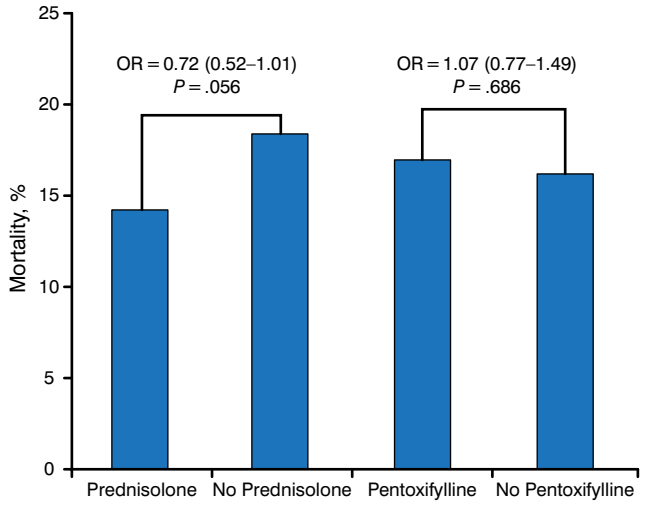
Figure 1. 28-Day Mortality



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