Table 1. Primary and Secondary End Points

End Point	ARISE Trial: Results		
	Sebelipase Alfa, % (n = 36)	Placebo, % (n = 30)	*P* Value
ALT normalization	31	7	.027
Reduction in LDL	−28	−6	< .001
Reduction in non-HDL	−28	−7	< .001
AST normalization	42	3	< .001
Reduction in triglycerides	−25	−11	.038
Increase in HDL	20	−0.3	< .001
Liver fat content reduction	−32	−4	< .001
Improvement in steatosis	63	40	.422
Reduction in liver volume	−10.3	−2.7	.007[a]

ALT, alanine transaminase; ARISE, Acid Lipase Replacement Investigating Safety and Efficacy trial; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[a]Cannot be interpreted as significant due to a lack of statistical significance of the end point above, according to a prespecified fixed sequence testing methodology.

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Table 2. Additional Liver Assessments, ARISE Results

Secondary End Points	Sebelipase Alfa	Placebo	*P* Value
Secondary end points, %			
AST normalization	42	3	< .001
Improvement in steatosis	63	40	.422
Exploratory end points			
Mean change in AST U/L (%)	−42 (−44)	−6 (−7)	< .001
Mean change in GGT U/L (%)	−23 (−35)	−2 (−2)	< .001
GGT normalization[a], %	62	8	.011

ARISE, Acid Lipase Replacement Investigating Safety and Efficacy trial; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

[a]Of those patients with abnormal GGT at baseline (n = 25/66).

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ALT levels normalized in placebo-treated patients after they were switched to sebelipase alfa. Patients treated with sebelipase alfa had a sustained response and improvement in ALT up to week 36.

Consistent with other forms of enzyme replacement therapy, sebelipase alfa addresses the cause of LAL-D by replacing the deficient enzyme.

Sustained Virologic Response of 91% in Patients Infected With HCV Treated With DCV-TRIO

Written by Toni Rizzo

Twelve weeks of treatment with the all-oral combination of daclatasvir (DCV), asunaprevir (ASV), and beclabuvir (BCV) resulted in sustained virologic response (SVR12) rates of >92% in treatment-naïve patients with hepatitis C virus (HCV) genotype (GT) 1 and 100% in patients with HCV genotype 4 in phase 2 studies [Everson GT et al. AASLD. 2013 LB-1; Hassanein T et al. EASL. 2014]. The aim of the phase 3 UNITY-1 trial [NCT01979939], presented by Fred Poordad, MD, University of Texas Health Sciences Center, San Antonio, Texas, USA, was to evaluate this all-oral, ribavirin-free combination in noncirrhotic treatment-naïve and treatment-experienced patients with HCV GT 1 infection.

DCV is a pangenotypic (genotypes [GT] 1–6 in vitro and GT 1–4 in clinical trials) NS5A inhibitor with a low potential for drug–drug interactions. It is approved in Europe and Japan, and it is under regulatory review in the United States. ASV is an N53 protease inhibitor with clinical data available for GT 1 and 4. BCV is a nonnucleoside NS5B polymerase inhibitor with clinical data available for GT 1 and 4. DCV/ASV/BCV is coformulated as a twice-daily, fixed-dose combination (FDC).

In the UNITY-1 trial, 312 treatment-naïve patients and 103 treatment-experienced patients were treated with DCV 30 mg/ASV 200 mg/BCV 75 mg FDC (DCV-TRIO) for 12 weeks and followed through week 48. The primary end point was SVR12, defined as HCV RNA < lower limit of quantitation (LLOQ) at posttreatment week 12, in treatment-naïve patients. The secondary end point was SVR12 in treatment-experienced patients.

All enrolled patients were aged ≥18 years, the median age was 55 years, and 58% were male. All patients had HCV RNA ≥ 10 000 IU/mL. Most of the patients (73%) were infected with HCV GT 1a. Most treatment-naïve and treatment-experienced patients had the non-CC *IL28B* GT. Treatment was completed by 97% of the patients. Eight patients discontinued due to lack of efficacy. Overall, SVR12 was achieved by 91% of the patients.

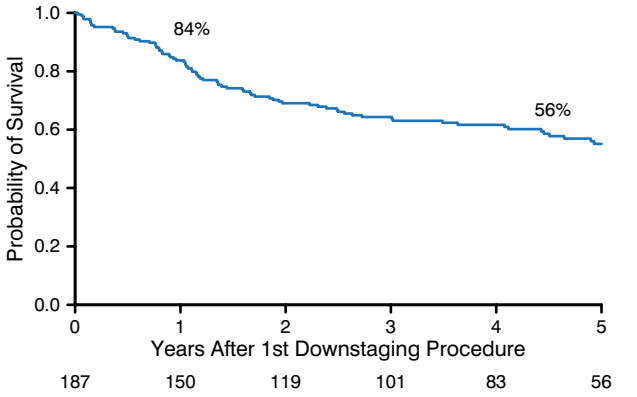
The SVR12 rate in treatment-naïve patients was 92%, significantly higher than the historic threshold rate of 79% (based on analysis of sofosbuvir plus peginterferon/ribavirin data). A significantly higher SVR12 rate of 89% was achieved in treatment-experienced

patients, compared with the historic threshold rate of 48% (based on analysis of simeprevir plus peginterferon/ribavirin data).

SVR12 rates of 98% to 100% were observed in treatment-naïve and treatment-experienced patients with HCV GT 1b. SVR12 rates were comparable with respect to gender, age, race, baseline HCV RNA, and *IL28B* genotype. On-treatment virologic breakthrough occurred in 2% of both treatment-naïve and -experienced patients. Posttreatment relapse occurred in 5% and 15% of treatment-naïve and -experienced patients, respectively. The most frequently observed resistance-associated variants among GT 1a patients were NS5A-Q30, NS3-R155, and NS5B-P495.

Treatment with the all-oral, ribavirin-free, fixed-dose DCV-TRIO for 12 weeks achieved an SVR12 of 91% in noncirrhotic patients with HCV genotype 1. DCV-TRIO was generally safe and well tolerated.

Figure 1. Intention-to-Treat Survival Following Liver Transplantation



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Uniform Downstaging Protocol Produces Excellent Posttransplantation Outcomes in HCC

Written by Nicola Parry

Neil Mehta, MD, University of California San Francisco, San Francisco, California, USA, presented the results of a multicenter study of downstaging of hepatocellular carcinoma (HCC) to within the Milan staging criteria before liver transplantation (LT), demonstrating excellent posttransplantation outcomes.

According to Dr Mehta, the Milan criteria represent the gold standard to select candidates for LT [Mazzaferro V et al. *N Engl J Med*. 1996]. He explained that downstaging of HCC represents a selection strategy involving expanded transplant criteria based on the control of tumor growth by locoregional therapy (LRT).

Currently in the USA, patients with HCC are only eligible for priority listing for LT with model for end-stage liver disease (MELD) exception if they meet stage T2 criteria.

Although downstaging to within Milan criteria has been shown to produce favorable post-LT outcomes in single-center studies, no multicenter studies have previously been reported. Consequently, this multicenter study aimed to evaluate post-LT and intention-to-treat outcomes under a uniform Region 5 downstaging protocol [Yao FY et al. *Hepatology*. 2008]. Successful downstaging was defined by having residual tumor within the Milan criteria.

The study enrolled 187 consecutive adult patients with HCC from 3 centers who were treated under the Region 5 downstaging protocol. Patients were included if they had 1 lesion > 5 cm and ≤ 8 cm; 2 or 3 lesions, each ≤ 5 cm, with the total diameter of all ≤ 8 cm; 4 or 5 lesions, each ≤ 3 cm, with the total diameter of all ≤ 8 cm; and no vascular invasion evident on imaging.

Of those who initially enrolled, 36.4% (n = 68) experienced dropout due to tumor progression or death at a median of 8 months from the first downstaging procedure. The probability of dropout from first downstaging was 26% at 1 year and 41% at 2 years, and the only significant predictors of dropout were Child-Pugh class B (P = .02) and C (P = .005) disease.

Successful downstaging was experienced by 63.6% (n = 119) of patients. Of these, 106 underwent deceased donor LT (DDLT), 3 underwent living donor LT, and 10 were awaiting DDLT at the end of study follow-up. The median time from first downstaging to LT was 12.6 months, with a median post-LT follow-up of 4.3 years.

Tumor characteristics were favorable at explant: 81% of patients overall were within Milan criteria, and 35% had complete tumor necrosis; of 71 patients with residual viable tumor, only 1 had a poorly differentiated tumor; and overall, only 6% of patients had microvascular invasion.

For the entire cohort, intention-to-treat survival was 84% at 1 year and 56% at 5 years (Figure 1).

Post-LT survival at was 95% at 1 year and 80% at 5 years. Of the 109 patients who underwent LT, 11% experienced HCC recurrence at a median of 19.1 months from transplantation.