SOF + GS-5816 100 mg (n = 27), or SOF + GS-5816 100 mg along with ribavirin (n = 26). The baseline demographics of the 4 study arms were comparable.

The viral kinetics of the 4 arms were similar, with HCV RNA descending to undetectable levels by week 2 of treatment. SVR12 for the SOF + GS-5816 25 mg arm was 100% (27/27) in the absence of ribavirin and 88% (21/24; 2 relapses and 1 discontinuation due to adverse event prior to decline of HCV RNA to an undetectable level) in the presence of ribavirin. SVR12 for the SOF + GS-5816 100 mg arm was 96% (26/27; consent withdrawn in 1 patient) in the absence of ribavirin and 100% (26/26) in the presence of ribavirin.

Adverse events were least frequent in the SOF + GS-5816 25 mg arm (18/27; 67%) compared with SOF + GS-5816 25 mg + ribavirin (19/24; 79%), SOF + GS-5816 100 mg (22/27; 81%), and SOF + GS-5816 100 mg + ribavirin (22/26; 85%). One serious adverse event occurred in the SOF + GS-5825 25 mg arm; it was not treatment related (noncompliance with seizure medication, seizure occurring after completing treatment). Adverse events occurring in more than 10% of patients were mild to moderate, similar in frequency between arms, and mainly comprised fatigue, headache, and nausea.

Ribavirin-containing treatments produced a decline in mean hemoglobin from weeks 2 to 8. Following treatment completion, the levels increased and were comparable with the other treatment arms.

The use of SOF + GS-5816 at 25 or 100 mg with or without ribavirin for 8 weeks yielded high SVR12 rates in treatment-naïve, noncirrhotic patients with HCV GT-3 infection. No virologic failures occurred in those receiving SOF + GS-5816 100 mg. Treatment was well tolerated. The results have prompted a phase 3 trial that will evaluate a ribavirin-free, fixed-dose combination of SOF 400 mg and GS-5816 100 mg.

Sebelipase Alfa Normalizes ALT and Multiple Other Disease-Related Abnormalities in Patients With LAL-D

Written by Maria Vinall

Lysosomal acid lipase deficiency (LAL-D) is an autosomal genetic recessive disorder that leads to an inability to break down lipid particles in the lysosome, and it is associated with early-onset cirrhosis and cardiovascular disease. Enzyme replacement therapy has been transformational for patients with LAL-D. Sebelipase alfa is a recombinant form of the human lysosomal acid lipase (LAL) enzyme used to replace the deficient enzyme in LAL-D.

The Acid Lipase Replacement Investigating Safety and Efficacy trial [ARISE; NCT01757184] was a randomized, double-blind, placebo-controlled phase 3 study designed to evaluate sebelipase alfa in 66 patients with LAL-D. Patients were randomized to receive 1 mg/kg sebelipase alfa or placebo every other week for 20 weeks during the double-blind phase, after which all patients continued on the study drug. LAL-D patients aged ≥ 4 years with an elevated alanine transaminase (ALT) level (≥ 1.5× the upper limit of normal) were enrolled and permitted to continue on stable doses of background lipid-lowering medications. Patients with a history of liver or hematopoietic stem cell transplant were excluded, as were those with Child–Pugh C status. The primary study end point was liver injury as measured by normalization of ALT. Other end points included the effect on lipid metabolism, as well as a reduction in liver volume and fat content.

Participants had a median age of 13 years, with the majority being younger than 18 years. As expected, the baseline serum transaminases in this group were elevated. Mean gamma-glutamyl transferase (GGT) was normal, whereas low-density lipoprotein (LDL) levels were very high (mean, 190 to 230 mg/dL). Baseline liver biopsy was available for 32 participants (mean age, 12 years). All of these patients had fibrosis; 47% had bridging fibrosis, and 31% cirrhosis. Dyslipidemia was present in 58% (38/66) of patients, including the 24% who were taking lipid-lowering medications.

Hierarchical fixed sequence testing was used to test across the secondary end points. In this method, if one of the secondary end points did not achieve significance, the subsequent end points were nullified. Treatment with sebelipase alfa was associated with ALT normalization in significantly more patients compared with placebo (31% vs 7%; $P = .027$). Patients treated with sebelipase alfa had a mean reduction in ALT units/L of 58 (53%) compared with 7 (6%) for placebo-treated patients ($P < .001$). Significant effects were also seen for 6 of the secondary end points (Table 1).

The reduction in ALT was accompanied by a reduction in liver fat content of 32% for patients treated with sebelipase alfa versus 4% for placebo-treated patients ($P < .001$). Other liver assessments are shown in Table 2.

Patients treated with sebelipase alfa also realized significant reductions in LDL (–28%) and increases in HDL (+20%) compared with placebo-treated patients (–6% and –0.3% LDL and HDL, respectively; both $P < .001$).

Most adverse events were mild and not related to the study drug. There were 2 serious adverse events in the sebelipase alfa group (an atypical infusion reaction and gastritis).

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

	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