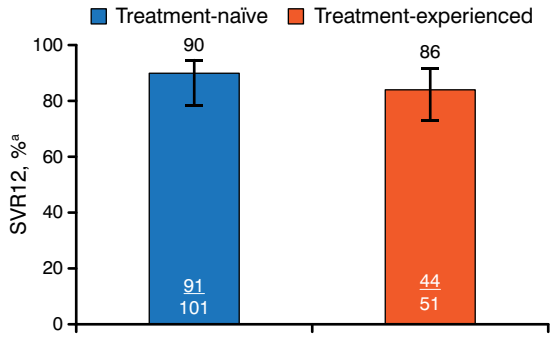
Figure 1. Primary End Point: Sustained Viral Response to Treatment 12 Weeks After Therapy



Error bars indicate 95% confidence intervals. SVR12, sustained viral response to treatment 12 weeks after therapy.

[a]Hepatitis C virus RNA < lower limit of quantification (25 IU/mL).

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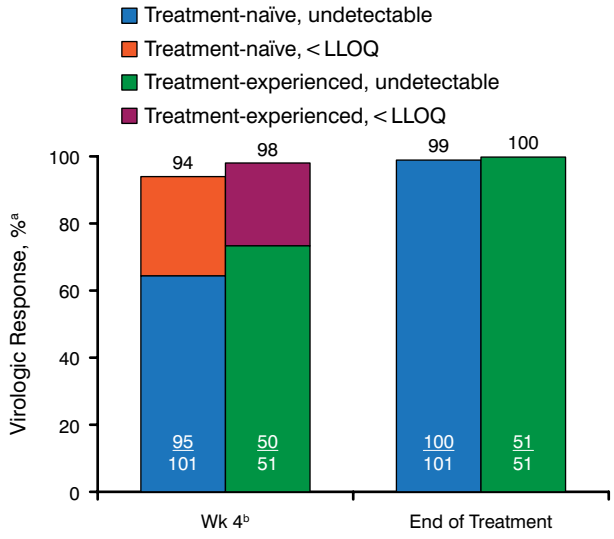
Figure 2. On-Treatment Virologic Response



HCV, hepatitis C virus; LLOQ, lower limit of quantification; SVR12, sustained viral response to treatment 12 weeks after therapy.

[a]Undetectable HCV RNA or HCV RNA < LLOQ (25 IU/mL).

[b]SVR12 rates based on week 4 HCV RNA levels: < LLOQ, target detected, 86%; < LLOQ, target not detected, 91%.

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Treatment with DCV plus SOF was associated with a high rate of SVR12 in both groups (Figure 1).

Figure 2 shows the on-treatment virologic response at week 4 and at the end of treatment for target not detected or target below the level of quantification. By the end of treatment, all but 1 patient were virus negative. Week-4 viral levels did not predict response vs nonresponse.

SVR12 rates were not influenced by sex, age < vs ≥ 65 years, HCV RNA levels, or IL28B polymorphism (CC vs non-CC). Cirrhosis did have a significant influence, regardless of prior treatment status. Overall, only 63% of patients with cirrhosis achieved SVR12 compared with 96% of patients without cirrhosis; rates were similar for treatment-naïve and experienced patients. Among patients with cirrhosis, 34% had portal hypertension (as assessed by platelet counts < 100 000/mm^2). Sixteen patients relapsed; 11 of those had cirrhosis. The most common adverse events (> 10% of patients) were headache, fatigue, and nausea; none led to discontinuation.

The combination of DCV plus SOF was safe, well tolerated, and associated with SVR12 rates as high as 96% in patients without cirrhosis. There were no virologic breakthroughs. The resistance analysis for this study is ongoing.

SOF Plus GS-5816 Effective in Noncirrhotic Patients Infected With HCV GT-3: ELECTRON-2 Final Results

Written by Brian Hoyle

An oral, once-daily, fixed-dose combination of the nucleotide polymerase inhibitor sofosbuvir (SOF) and nonstructural protein 5A (NS5A) inhibitor GS-5816 (ledipasvir) provided for 8 weeks with or without ribavirin to noncirrhotic patients infected with hepatitis C virus (HCV) genotype 3 (GT-3) yields high rates of sustained virological response 12 weeks after therapy (SVR12). The final results of the phase 2 ELECTRON-2 study were presented by Edward Gane, MD, Auckland Clinical Studies, Auckland, New Zealand.

SOF has potent activity against HCV [Jacobson IM et al. *New Engl J Med.* 2013; Lawitz E et al. *New Engl J Med.* 2013]. Unpublished studies presented at the European Association for the Study of the Liver annual meeting have also indicated the anti-HCV activity of GS-5816, and the high SVR following a 12-week regimen in noncirrhotic, treatment-naïve HCV patients. These studies spurred the phase 2, open-label, ELECTRON-2 study evaluating the efficacy and safety of an 8-week regimen of SOF + GS-5816 in noncirrhotic, treatment-naïve patients infected with HCV GT-3. The primary efficacy end point was SVR12 with a lower limit of quantitation of HCV RNA of 15 IU/mL. The primary safety end points were adverse events and laboratory abnormalities.

Subjects received SOF + GS-5816 25 mg (n = 27), SOF + GS-5816 25 mg along with ribavirin (n = 24),

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).