The overall recurrence-free probability was 95% at 1 year, and 87% at 5 years from transplantation. The only significant predictors of HCC recurrence were alpha-fetoprotein > 500 ng/mL (P = .003) and microvascular invasion (P = .002). No center-specific differences seen in intention-to-treat survival, post-LT survival, and overall recurrence-free probability of the cohort.

Data from this largest study to date, and the first multicenter study, demonstrated successful downstaging of HCC to within the Milan criteria in almost two-thirds of patients. These results support broader application of this uniform downstaging protocol, concluded Dr Mehta.

SOF Plus GS-5816 Effective in Noncirrhotic, Treatment-Naïve Patients Infected With HCV Genotypes 1 to 6

Written by Brian Hoyle

An oral, once-daily, 12-week, fixed-dose combination of the nucleotide polymerase inhibitor sofosbuvir (SOF) and nonstructural protein 5A (NS5A) inhibitor GS-5816 (ledipasvir) yields high rates of sustained virological response 12 weeks after therapy (SVR12) in noncirrhotic patients infected with genotypes 1 to 6 of hepatitis C virus (HCV). The results of the open-label study were presented by Tram Tran, MD, Cedars-Sinai Hospital, Los Angeles, California, USA.

The prowess of SOF against HCV is known [Jacobson IM et al. *New Engl J Med.* 2013; Lawitz E et al. *New Engl J Med.* 2013]. High SVR following a 12-week GS-5816 regimen in noncirrhotic, treatment-naïve HCV genotype 1 to 6 patients has been described.

In part A of the current study, patients infected with HCV genotype 1 (n = 55), genotype 3 (n = 54), and genotypes 2, 4, 5, and 6 (n = 45) received oral, ribavirin-free, once-daily SOF + GS-5816 25 mg or 100 mg for 12 weeks. SVR12 was consistently high for the 25-mg and 100-mg doses: genotype 1 (26/27, 96% and 28/28, 100%), genotype 2 (10/11, 91% and 10/10, 100%), genotype 3 (25/27, 93% and 25/27, 93%), genotype 4 (7/7, 100% and 6/7, 86%), genotype 5 (25 mg only: 1/1, 100%), and genotype 6 (4/4, 100% and 5/5, 100%). The relatively lower SVR12 for the 100-mg genotype 4 patients reflected the loss of 1 patient to follow-up.

Part B of the study focused on genotype 1 (n = 120) and 2 (n = 103) noncirrhotic, treatment-naïve patients and involved an 8-week treatment with the 25-mg and 100-mg doses of SOF + GS-5816 without or with (1000 to 1200 mg/d) ribavirin.

The primary objective of part B was the evaluation of safety (adverse events [AEs], laboratory abnormalities) and efficacy. The primary efficacy end point was SVR12, with an HCV RNA lower limit of 25 IU/mL.

Demographics of the 4 treatment arms were similar. The completion rate was 98% to 100%, with 1 discontinuation because of an AE in the SOF + GS-5816 25 mg arm and 1 case of noncompliance in the SOF + GS-5816 100 mg + ribavirin arm.

SVR12 in genotype 1 patients receiving the 25-mg dose without and with ribavirin was 87% (26/30; 3 relapses and 1 AE-related discontinuation) and 83% (25/30; 5 relapses), respectively. The respective value for the 100-mg dose was 90% (26/29; 3 relapses) and 81% (25/31; 5 relapses and 1 lost to follow-up). SVR12 in genotype 2 patients receiving the 25-mg dose without and with ribavirin was 77% (20/26; 6 relapses) and 88% (22/25; 2 relapses and 1 lost to follow-up), respectively. The respective value for the 100-mg dose was 88% (23/26; 3 relapses) and 88% (23/26; 3 relapses).

AEs were similar in the 4 arms. The 4 grade 3 to 4 AEs in the SOF + GS-5816 25 mg arm were not treatment related. Relatively frequent AEs mainly comprised fatigue, headache, nausea, and nasopharyngitis. They were manageable.

The 12-week regimen produced SVR12 rates exceeding 90% in all HCV genotypes. The 8-week regimen was less effective, with lower SVR rates and higher relapse rates in HCV genotype 1 and 2 patients. Inclusion of ribavirin did not affect safety and tolerability. SOF 400 mg and GS-5816 100 mg have been coformulated in a fixed-dose combination for a phase 3 study.

Terlipressin and Albumin Combination Therapy Improves Renal Function in HRS-1

Written by Nicola Parry

Thomas D. Boyer, MD, University of Arizona, Tucson, Arizona, USA, presented initial data from A Placebo-Controlled, Double-Blind Study to Confirm the Reversal of Hepatorenal Syndrome Type 1 With Terlipressin [REVERSE; NCT01143246], the largest trial to date in type 1 hepatorenal syndrome (HRS-1) using terlipressin. The results demonstrated that terlipressin plus albumin treatment improved renal function in patients with HRS-1 when compared with albumin alone.

According to Dr Boyer, HRS-1 involves the development of renal failure in patients with liver cirrhosis due

to a sequence of events beginning with portal hypertension and development of a hyperdynamic circulation, leading to splanchnic and systemic vasodilation, and ultimately renal vasoconstriction.

Terlipressin is an arginine vasopressor (V1) receptor agonist that causes splanchnic and systemic vasoconstriction, redistributing blood to the arterial circulation, thereby improving renal perfusion. Albumin also augments this effect by helping to maintain the enhanced arterial blood volume.

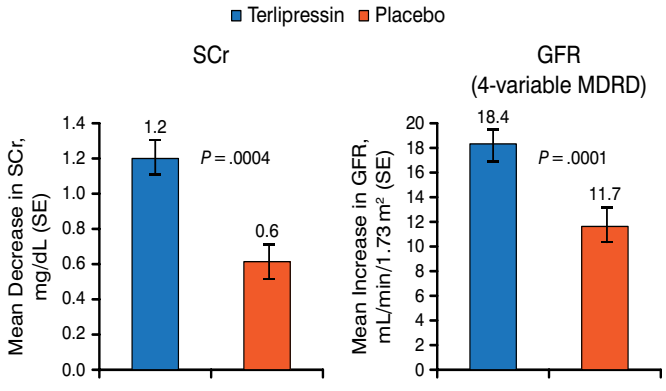
The REVERSE trial was a randomized, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy of terlipressin plus albumin for the treatment of HRS-1.

The primary end point was confirmed HRS reversal (CHRSR), defined as the number of patients with 2 serum creatinine values ≤1.5 mg/dL at least 48 hours apart while on treatment. Secondary end points included HRS reversal (1 serum creatinine value ≤1.5 mg/dL) and change in renal function as assessed by changes in serum creatinine.

Patients with HRS-1 were randomized 1:1 to treatment with terlipressin plus albumin (n=93) or placebo (albumin alone; n=95).

The primary end point of CHRSR was not met in the trial (19.6% vs 13.1%; $P=.221$). However, with respect to secondary end points, there was significant improvement in renal function in patients in the terlipressin group, with greater mean decreases in serum creatinine from baseline through the end of the study (1.2 vs 0.6 mg/dL; $P=.0004$). This corresponded to a significant increase in glomerular filtration rate with terlipressin (18.4 vs 11.7 mL/min/1.73 m^2; $P=.0001$; Figure 1).

Figure 1. Improvement in Renal Function in the REVERSE Trial



SCr, serum creatinine; GFR, glomerular filtration rate; SE, standard error; MDRD, modification of diet in renal disease.

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Improvements in serum creatinine were also found to correlate with patient survival at 90 days ($P<.0001$).

There was no significant difference in HRS reversal between the groups (23.7% vs 15.2%; $P=.130$).

The need for renal replacement therapy (RRT) was similar between the 2 groups. Among patients with CHRSR, none in the terlipressin group required RRT by 90 days, compared with about 25% of those who received placebo. The response to terlipressin may therefore be more durable, Dr Boyer suggested.

Overall survival was similar in both groups, with approximately half of the patients (56 vs 53) remaining alive at 90 days.

The incidence of adverse events (AEs) was consistent with those reported in previous trials using terlipressin. Additionally, as expected with the use of a vasoactive drug, significantly more patients in the terlipressin group required treatment discontinuation because of AEs (20.4% vs 6.3%; $P=.008$).

Dr Boyer concluded that terlipressin treatment has a favorable benefit-risk profile in HRS-1, and, compared with placebo, is associated with significant improvement in renal function that also correlates with improved survival.

Direct-Acting Antiviral Therapy Produces High SVR12 in HCV GT-1 Cirrhotic Patients Regardless of Baseline Characteristics

Written by Brian Hoyle

Treatment of cirrhotic, hepatitis C virus (HCV) genotype 1 (GT-1)-infected patients with a twice-daily oral regimen involving a single tablet of 3 direct-acting antiviral agents – the HCV NS3/4A serine protease inhibitor ABT-450 at 150 mg plus ritonavir 100 mg plus the NS5A inhibitor ombitasvir 25 mg – along with a tablet of dasabuvir 250 mg and a tablet of ribavirin yields high rates of sustained virologic response 12 weeks following conclusion of treatment (SVR12). The high SVR12 rates occur regardless of the baseline characteristics of the patients. The findings of the large, international, phase 3 TURQUOISE-II trial were presented by Michael Fried, MD, University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA. The findings of the TURQUOISE-II have been published [Poordad F et al. *New Engl J Med.* 2014].

Cirrhosis, high-level HCV viremia, and interleukin 28B (IL28B) non-CC genotype have been linked with lower SVR rates [Manns M et al. *Lancet* 2014]. These data, however, have come from small patient subsets,