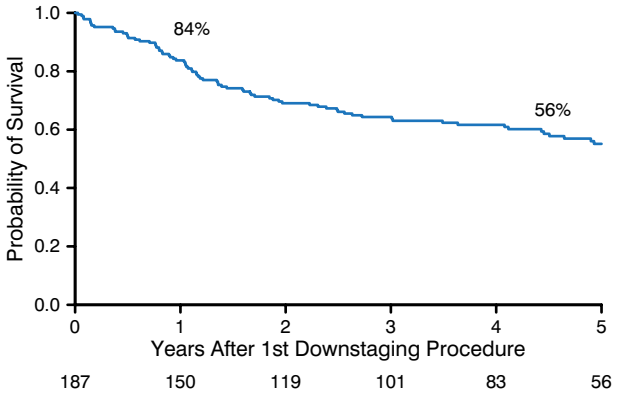
patients, compared with the historic threshold rate of 48% (based on analysis of simeprevir plus peginterferon/ribavirin data).

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



Reproduced with permission from N Mehta, MD.

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.

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