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.

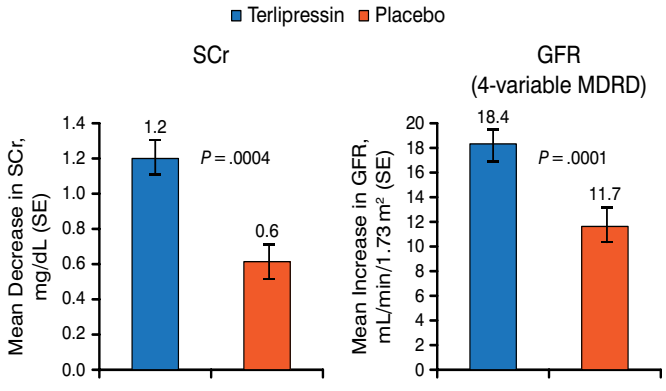
The REVERSE trial was a randomized, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy of terlipressin plus albumin for the treatment of HRS-1.

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,

and information on SVR rates in difficult-to-treat populations, like null responders, is scant [Afdhal N et al. *New Engl J Med.* 2014]. TURQUOISE-II sought to evaluate the influence of baseline characteristics on treatment outcomes in HCV GT-1-infected patients with compensated cirrhosis. Patients (n = 380) were randomized to treatment with the direct-acting antiviral regimen of ABT-450 plus ritonavir plus ombitasvir along with dasabuvir, with the inclusion of 1000 or 1200 mg ribavirin according to body weight, for either 12 weeks (n = 208) or 24 weeks (n = 172). SVR 12 was assessed at week 24 and 36.

All included patients had received ≥ 1 dose of the drugs. Influential factors that were examined included viral factors (HCV RNA level, HCV subtype), host factors (age, sex, body mass index (BMI), IL28B genotype status, prior treatment, and histories of diabetes, depression/bipolar disorder, and intravenous drug use), and disease factors (serum albumin, platelet count, serum alpha-fetoprotein).

Baseline characteristics in the 12- and 24-week arms were comparable in terms of sex, ethnicity, mean age, mean BMI, IL28B non-CC genotype, treatment-naïve/experienced proportions, platelet count, serum albumin, and Child-Pugh score. The overall SVR12 rates were high.

SVR12 was achieved in 91.6% (239/261) and 99.2% (118/119) of the genotype 1a and 1b patients, respectively. The rate was not significantly lower in the 12-week arm (91.8%; 191/208) compared with the 24-week arm (96.5%; 166/172). Consistently high viral response rates were evident at 12 and 24 weeks according to age (< 65 years and ≥ 65 years), sex (male and female), body mass index (< 30 kg/m^2 and ≥ 30 kg/m^2), interleukin 28-B (IL28B) genotype, HCV subtype, baseline viral load (< 800 000 IU/mL and ≥ 800 000 IU/mL), prior peglyated interferon and ribavirin treatment, alfa-fetoprotein (< 20 ng/mL and ≥ 20 ng/mL), and histories of diabetes, intravenous drug use, and depression/bipolar disorder.

SVR12 was not achieved in 23 patients (17 in the 12-week arm and 6 in the 24-week arm). Associated factors as determined in a logistic regression analysis were IL28B TT genotype ($P = .021$), prior null response ($P = .038$), and HCV genotype 1a ($P = .046$). Trends were evident for alfa-fetoprotein ($P = .059$) and treatment duration ($P = .066$). Overall, 2.1% of patients discontinued treatment because of adverse events.

The interferon-free regimen comprising the direct-acting antiviral regimen of ABT-450 plus ritonavir plus ombitasvir along with dasabuvir, plus ribavirin produced high SVR12 rates in a broad range of treatment-naïve and -experienced cirrhotic patients. Importantly, host, viral, and disease characteristics were not influential.

Myrcludex B Therapy Reduced HBV DNA and HDV RNA in Phase 2a Clinical Trial

Written by Toni Rizzo

Chronic hepatitis B virus (HBV) infection is rarely cured with current therapies, and there is no effective therapy for hepatitis D virus (HBD) coinfection. Myrcludex B is a first-in-class entry inhibitor that inactivates the HBV and HDV receptor sodium taurocholate cotransporting polypeptide (NTCP). Myrcludex B specifically targets NTCP at the hepatocyte surface, inhibiting HBV and HDV receptor function and NTCP-mediated bile salt uptake into hepatocytes. Phase 1 clinical trials have demonstrated the safety of Myrcludex B.

The objective of the phase 2a study, presented by Stephan Urban, MD, University Hospital Heidelberg, Heidelberg, Germany, was to evaluate the safety, tolerability, and antiviral efficacy of Myrcludex B. The study included 2 cohorts. Cohort A consisted of 40 hepatitis B e antigen-negative patients with chronic HBV infection, HBV DNA > 2000 IU/mL, median HBV DNA 4.7 $\log_{10}$ IU/mL, and no cirrhosis. These patients were treated for 12 weeks with once-daily subcutaneous Myrcludex B at 0.5 mg, 1 mg, 2 mg, 5 mg, or 10 mg doses (n = 8/dosage group). Treatment was extended to 24 weeks for patients in the 10 mg group. Cohort B included 24 patients with HDV and compensated liver disease scheduled for 48 weeks of pegylated interferon-alpha (PEG-IFNα) therapy. Eight patients were pretreated with Myrcludex B 2 mg alone for 24 weeks (Cohort B1). Eight patients were treated with PEG-IFNα plus Myrcludex B for the first 24 weeks (Cohort B2), and the 8 remaining patients were treated with PEG-IFNα alone (Cohort B3). The end points for both cohorts were biochemical and virologic response, immunogenicity, bile salt elevations, pharmacokinetics, and safety and tolerability.

HBV DNA levels declined during Myrcludex B treatment in all groups. A pronounced effect of > 1 $\log_{10}$ HBV reduction occurred in 6 patients in the 10 mg dose group and in 7 patients in the lower-dosing groups.

Myrcludex B had no significant effect on hepatitis B surface antigen (HBsAg) serum levels during treatment. At week 24, a > 1 $\log_{10}$ HDV RNA reduction occurred in 6 Cohort B1 patients during Myrcludex B monotherapy and 7 Cohort B2 patients during combination therapy. HDV RNA became negative in 2 patients during Myrcludex B monotherapy and in 5 patients receiving combination therapy. Myrcludex B induced preS-specific antibodies in 4 patients during Myrcludex monotherapy and in 7 patients during combination therapy.