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.

Treatment with Myrcludex B normalized alanine aminotransferase (ALT) levels in 55% of patients; median ALT levels declined from 76 U/L to 36 U/L at week 12 ($P < .001$). Myrcludex B had a dose-dependent effect on serum bile salt levels. Rapid elevation of taurocholic acid and glyocholic acid were observed with Myrcludex B >1 mg/day. Myrcludex B withdrawal resulted in rapid bile salt normalization.

Adverse events included injection-site dermatitis (n=3, 10 mg group) and psoriasis exacerbation leading to discontinuation (n=1, Cohort B2).

The investigators concluded that Myrcludex B was safe and well tolerated in HBsAg-positive patients with or without HDV coinfection. HBV entry inhibition was associated with HBV DNA and strong HDV RNA declines and improved biochemical disease activity.

SVR After Treatment of HCV Genotype 1a With ABT-450/Ritonavir, Ombitasvir, and Dasabuvir Is Enhanced by RBV in Noncirrhotic Patients and by Extension of Duration in Cirrhotic Patients

Written by Brian Hoyle

A 3-drug (3D) regimen of ABT-450, an NS3/4A protease inhibitor, co-dosed with ritonavir, ombitasvir, an NS5A inhibitor, and dasabuvir, a non-nucleoside NS5B polymerase inhibitor has been given alone or in combination with ribavirin (RBV) and studied in 6 phase 3 trials of more than 2700 patients. The 3D regimen is safe and effective in patients infected with hepatitis C virus (HCV) genotype 1a with or without cirrhosis. However, efficacy of this treatment may be variably influenced by HCV genotype subtype, treatment experience (naïve vs experienced), and stage of fibrosis (early fibrosis vs cirrhosis).

In this analysis, data from 1058 patients with HCV genotype 1a from 4 phase 3 trials were pooled to examine the impact of RBV in noncirrhotic patients and treatment duration in cirrhotic patients. The studies were SAPPHIRE-I and -II [Feld JJ et al. *N Engl J Med*. 2014; Zeuzem S et al. *N Engl J Med*. 2014], PEARL-IV [Ferenci P et al. *N Engl J Med*. 2014], and TURQUOISE-II [Poordad F et al. *N Engl J Med*. 2014] (Table 1). Gregory Everson, MD, University of Colorado, Denver, Colorado, USA, presented the results.

Key inclusion criteria for this study were chronic HCV infection with genotype 1a, age 18 to 70 years, and plasma HCV RNA >10 000 IU/mL. Key exclusion criteria were infection with hepatitis B virus or human immunodeficiency virus.

Table 1. The Pooled Studies

	Patients Without Cirrhosis, n (%)		Patients With Cirrhosis, n (%)	Total, n (%)
	3D + RBV (n = 593)	3D + PBO (n = 202)	3D + RBV (n = 263)	3D ± RBV (n = 1058)
Treatment-naïve	420 (71)	202 (100)	122 (46)	744 (70)
Treatment-experienced	173 (29)	0	141 (54)	314 (30)

3D, 3-drug direct-acting antiviral regimen; GT1a, genotype 1a; PBO, placebo; RBV, ribavirin.
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PATIENTS WITHOUT CIRRHOSIS

The 3D regimen was administered for 12 weeks with or without RBV. Overall, the rates of SVR12 with and without RBV were 96.0% (569/593) and 90.1% (182/202) ($P = .004$). In treatment-naïve patients, rates of SVR12 were 96.0% (403/420) and 90.1% (182/202) ($P = .006$), respectively. All treatment-experienced patients were given RBV, and rates of SVR12 were 94% for relapsers, 100% for partial responders, and 95.4% for null responders. RBV dose modification was required in 6.7% of RBV-treated patients, but, despite the dose modification, 97.6% of these patients achieved SVR12. In multivariable analyses, high baseline body mass index and RBV-free treatment were associated with lower likelihood of achieving SVR12 ($P = .005$ and $P = .007$, respectively). Adverse events and related discontinuations were generally mild and were more common in RBV-containing treatment.

PATIENTS WITH CIRRHOSIS

All of the patients with cirrhosis were treated with RBV, and treatment durations of 12 and 24 weeks were compared (Figure 1). The overall rates of SVR12 were 88.7% for 12 weeks and 95% for 24 weeks ($P = .08$). The lower SVR12 with 12 weeks was mainly evident in the treatment-experienced patients with prior null response, 80.0% versus 92.9% for 12 versus 24 weeks of treatment ($P = .13$). Rates of SVR12 in the treatment-naïve patients were 92.4% and 94.6% for 12 and 24 weeks of treatment, respectively.

In multivariable analyses, the TT IL28B genotype and a prior null response to peginterferon/RBV therapy were associated with failure to achieve SVR12 ($P = .008$ and