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.
Reproduced with permission from G Everson, MD.

PATIENTS WITHOUT CIRRHOSIS

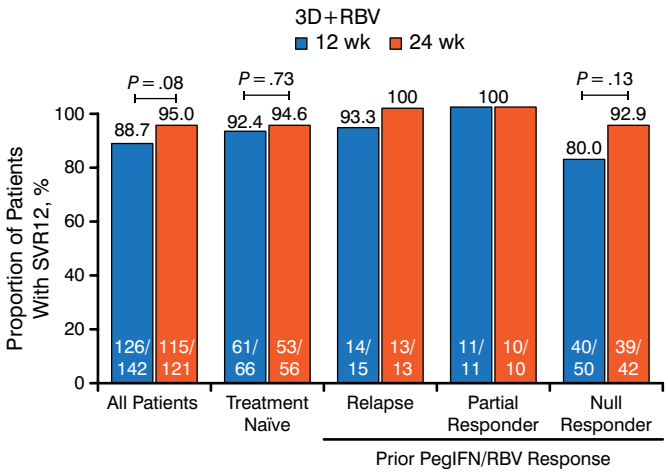
The 3D regimen was administered for 12 weeks with or without RBV. Overall, the rates of SVR12 with and without RBV were 96.0% (569/593) and 90.1% (182/202) ($P = .004$). In treatment-naïve patients, rates of SVR12 were 96.0% (403/420) and 90.1% (182/202) ($P = .006$), respectively. All treatment-experienced 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

Figure 1. SVR12 Rates in Cirrhotic HCV1a-Infected Treatment-Naïve and Treatment-Experienced Patients Treated for 12 or 24 Weeks



3D, 3-drug direct-acting antiviral regimen; HCV1a, hepatitis C virus genotype 1a; PegIFN, pegylated interferon; RBV, ribavirin; SVR12, sustained virologic response at week 12.

P=.009, respectively). Adverse events and event-related discontinuation were similar for both treatment durations.

This pooled analysis of 4 phase 3 trials of patients infected with HCV genotype 1a indicates that the rate of SVR in noncirrhotic patients treated with the 3D regimen may be enhanced by addition of RBV. In addition, in patients with cirrhosis, extension of 3D + RBV to 24 weeks may be warranted, especially for those who were prior null responders to peginterferon/RBV.

HCV–Infected Patients With Compensated Cirrhosis Benefit From 12-Week, Once-Daily, Oral Combination of LDV and SOF

Written by Brian Hoyle

The once-daily, oral, 12-week regimen using a single tablet combination of the nonstructural protein 5B (NS5B) inhibitor sofosbuvir (SOF; 400 mg) and the NS5A inhibitor ledipasvir (LDV; 90 mg) with or without ribavirin (RBV) produces high sustained virologic response 12 weeks after conclusion of treatment (SVR12) in hepatitis C virus (HCV)-infected patients with compensated cirrhosis, according to Marc Bourlière, Hôpital Saint Joseph, Marseilles, France. Inclusion of RBV can boost the SVR12 at the expense of increased adverse events and declined hemoglobin count. The LDV plus SOF regimen, recently approved by the Food and Drug Administration for the treatment of chronic HCV genotype 1 infection, is safe and well tolerated in cirrhotic patients.

The present study used pooled data from the phase 2 LONESTAR trial [Lawitz E et al. *Lancet* 2014], phase 2 ELECTRON and ELECTRON-2 trials [NCT01260350], phase 3 GS-US-337-0113 [NCT01975675], phase 3 ION-1 trial [Afdhal N et al. *N Engl J Med.* 2014], phase 3 ION-2 trial [Afdhal N et al. *N Engl J Med.* 2014], and phase 3 SIRIUS trial [NCT02073656]. The primary end point after a 12- or 24- week treatment with LDV plus SOF ± RBV was SVR12.

Of the 513 HCV infected patients, 161 were treatment naïve and 352 were treatment experienced. They were comparable at baseline concerning mean age, gender, ethnicity, mean body mass index, proportions of interleukin 28B (IL28B) CC genotype and genotype 1a, mean HCV RNA, and laboratory data. The majority (68%) of treatment-experienced patients had a prior failure of protease inhibitor therapy. SVR12 was high overall and in the 12- and 24-week groups.

Twenty of the 513 patients (3.9%) failed to achieve SVR12. Of these, 18 relapsed, 1 was lost to follow-up, and 1 died (likely from an infection). SVR12 was not influenced by age, treatment duration, and/or the absence/presence of RBV, with the exception of treatment-experienced patients treated for 12 weeks with LDV plus SOF. Genotype in both the absence and presence of RBV was not influential. For treatment-experienced patients, prior failure of protease inhibitor therapy was not influential. Lower SVR12 was noted in patients with a platelet count $< 75 \times 10^3$ per µL.

The inclusion/absence of RBV had no effect on the frequency of adverse events in general and on grade ≥ 3 adverse events. RBV was associated with more adverse events that prompted discontinuation (n = 3, 1% vs n = 38, 15%) and decline of hemoglobin to < 10 g/dL (n = 1, < 1%, versus n = 26, 10%). Adverse events occurring in more than 10% overall and in either patient group predominantly included headache, fatigue, asthenia, insomnia, and nausea. The presence of RBV was associated with a greater prevalence of pruritus and rash.

The pooled data revealed an SVR12 of 96% overall. In treatment-experienced patients, the 12-week LDV plus SOF regimen produced a 90% SVR12. The rate was boosted to ≥ 96% by the inclusion of RBV at the expense of more frequent adverse events and hemoglobin decline. The LDV plus SOF combination is thus judged to be safe and effective for HCV-infected patients with compensated cirrhosis. The similar findings from the 12- and 24-week treatments indicate that the shorter treatment period is acceptable.