Analysis of SVR Rates Across Populations With Multiple Negative Predictors

Written by Jaye Summers

The multitargeted regimen of 3 direct-acting antivirals—ombitasvir (an NS5A inhibitor), dasabuvir (a nonnucleoside NS5B RNA polymerase inhibitor), and paritaprevir (an NS3/4A protease inhibitor boosted with ritonavir), with or without ribovarin—has demonstrated high efficacy in 6 phase 3 clinical trials encompassing >2000 patients with genotype 1 hepatitis C virus (HCV; Table 1).

Nancy Reau, MD, The University of Chicago Medicine, Chicago, Illinois, USA, presented a composite review of data from the 6 trials that examined whether multiple predictors of response had a meaningful impact on sustained virologic response at week 12 (SVR12). These predictors—traditionally associated with less robust clinical outcomes in patients with HCV—include cirrhosis, high baseline viral load, weight, *IL28B* non-CC genotype, and prior treatment failure.

A multivariate stepwise logistic regression was performed on data from the 2053 patients who participated in all 6 trials. The analysis included 22 continuous and categorical variables performed on 2 populations: (1) all patients who had data available regardless of whether they had received a label-recommended regimen and (2) patients who received a label-recommended regimen by HCV subgenotype and cirrhosis status.

Analysis of the entire cohort found that while genotype 1a disease was independently and significantly associated with reduced SVR12 (94%; $P<.001$), the SVR12 rate for genotype 1b was 99%. Other factors associated with significantly lower SVR12 included higher weight at baseline ($P=.007$), *IL28B* TT genotype ($P=.034$), Hispanic/Latino ethnicity ($P=.013$), and higher baseline HCV RNA ($P=.041$). Traditional factors associated with lower cure rates, such as the presence of cirrhosis and prior treatment response, were not associated with lower SVR rates.

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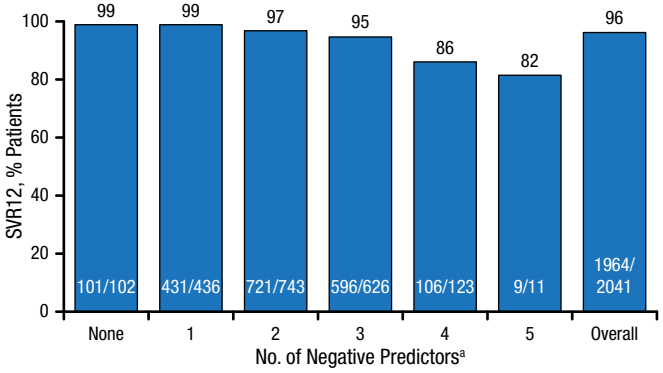
Table 1. Overview of Treatment Regimens and SVR12 Rates in 6 Phase 3 Trials

Trial					
Regimen	**n**	**GT**	**PegIFN/RBV[a]**	**Cirrhosis**	**SVR12, %**
SAPPHIRE-I [Feld JJ et al. *N Engl J Med.* 2014]					
3D + RBV for 12 wk	473	1a, 1b	No	No	96.4
SAPPHIRE-II [Zeuzem S et al. *N Engl J Med.* 2014]					
3D + RBV for 12 wk	297	1a, 1b	Yes	No	96.3
PEARL-II [Andreone P et al. *Gastroenterology.* 2014]					
3D for 12 wk	91	1b	Yes	No	100
3D + RBV for 12 wk	88				97.7
PEARL-III [Ferenci P et al. *N Engl J Med.* 2014]					
3D for 12 wk	209	1b	No	No	99.0
3D + RBV for 12 wk	210				99.5
PEARL-IV [Ferenci P et al. *N Engl J Med.* 2014]					
3D for 12 wk	205	1a	No	No	90.2
3D + RBV for 12 wk	100				97.0
TURQUOISE-II [Poordad F et al. *N Engl J Med.* 2014]					
3D + RBV for 12 wk	208	1a, 1b	Yes and no	Yes	91.8
3D + RBV for 24 wk	172				96.5

3D, regimen of 3 direct-acting antivirals (ombitasvir, dasabuvir, and paritaprevir boosted with ritonavir); GT, genotype; PegIFN/RBV, pegylated interferon/ribovarin; SVR12, sustained virologic response for 12 wk.

[a]Treatment experienced.

Figure 1. SVR12 Rates per Cumulative Number of Negative Predictors



HCV, hepatitis C virus; SVR12, sustained virologic response for 12 wk.

[a]Negative predictors: HCV genotype 1a, weight ≥ 75 kg, *IL28B TT*, Hispanic/Latino, HCV RNA ≥ 800 000 IU/mL.

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Table 2. Label-Recommended Regimens

	Patients Without Cirrhosis		Patients With Cirrhosis	
	GT1a	GT1b	GT1a	GT1b
Regimen	3D + RBV	3D	3D + RBV	3D + RBV
Duration, wk	12	12	24	12

US product insert and European Union summary of product characteristics–recommended regimens for subjects with GT1 infection.

3D, regimen of 3 direct-acting antivirals (ombitasvir, dasabuvir, and paritaprevir boosted with ritonavir); GT, genotype; RBV, ribovarin.

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The SVR12 rates for the entire cohort by the cumulative number of individual negative predictors are shown in Figure 1.

Among >2000 patients in the studies, 1083 received the label-recommended regimen (Table 2). The overall rate of SVR12 among those patients was 97% (n = 1052), with rates similarly high regardless of whether cirrhosis was present. Only 1 patient with a genotype 1b infection did not achieve SVR12. Of the 31 patients who did not achieve SVR12, 19 (1.8%) had on-treatment breakthrough or posttreatment relapse; 12 (1.1%) discontinued treatment prematurely. Of these 12 discontinuations, 3 were due to adverse events. Of the 22 variables, only body mass index and HCV genotype 1a disease had a negative impact in the multivariate stepwise analysis.

According to Dr Reau, these data suggest that the regimen of 3 direct-acting antivirals with or without ribovarin confers high SVR12 rates and offers an effective treatment option for patients with HCV who present with factors previously thought to have an negative impact on treatment response.

ALLY 2: Daclatavir + Sofosbuvir Effective in Treating HIV/HCV Coinfected Patients

Written by Brian Hoyle

Kenneth Sherman, MD, PhD, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA, presented the findings of ALLY 2 [NCT02032888], a phase 3, randomized, open-label clinical trial, which demonstrated a sustained virologic response for 12 weeks (SVR12) in 97% of patients coinfected with genotypes 1 to 4 hepatitis C virus (HCV) and HIV. Patients were treated with the NS5A inhibitor daclatasvir (DCV) and NS5B inhibitor sofosbuvir (SOF), which allowed for treatment without having to modify the combination antiretroviral therapy (cART) regimen.

About 130 to 150 million people are infected with chronic HCV worldwide [WHO. http://www.who.int/mediacentre/factsheets/fs164/en/. Accessed June 3, 2015], including an estimated 3 to 4 million in the United States [CDC. http://www.cdc.gov/hepatitis/hcv/statisticshcv.htm. Accessed June 3, 2015]. Up to 20% of people with chronic HCV will develop cirrhosis, with about the same proportion progressing to liver cancer [WHO. http://www.who.int/mediacentre/factsheets/fs164/en/. Accessed June 3, 2015].

HIV/HCV coinfection accelerates progression of HCV liver disease [Macías J et al. *Hepatology.* 2009] and hinders pegylated interferon treatment [Grint D et al. *HIV Med.* 2013]. A treatment regimen directed at HIV/HCV co-infected patients must not compromise cART. The positive efficacy and safety results of the DCV + SOF combination in chronic HCV monoinfection [Sulkowski MS et al. *N Engl J Med.* 2014] prompted ALLY 2, which evaluated the combination treatment in HIV/HCV coinfected patients on a broad range of antiretroviral therapies.

The ALLY 2 trial involved 203 patients who were treatment-naïve for HCV (n = 151) or who had been treated previously (n = 52). The treatment-naïve patients were randomized 2:1 to DCV 30/60/90 mg plus SOF 400 mg QD for either 12 weeks (n = 101) or 8 weeks (n = 50). The treatment-experienced patients received 12 weeks of therapy. The standard DCV dose was 60 mg, with the dose being adjusted according to cART: 30 mg in those receiving ritonavir-boosted protease inhibitors and 90 mg when cART included nonnucleoside reverse transcriptase inhibitors, except for rilpivirine. At baseline, the 3 arms were comparable in demographic, clinical, and prior HIV treatment characteristics. The primary end point, SVR12 in the treatment-naïve patients with HCV genotype 1 treated for 12 weeks, was 96% (Figure 1).

Patients with baseline NS5A resistant-associated variants achieved SVR12 at a rate of 96% (22/23) when treated