

Future Directions for HCV Therapy

Characteristics of an Ideal Combination DAA Regimen^{1,2}

All oral (IFN-free) and ribavirin-free

Potent (>90% SVR)

Pan-genotypic

Short duration (≤ 12 weeks)

Safe

Convenient

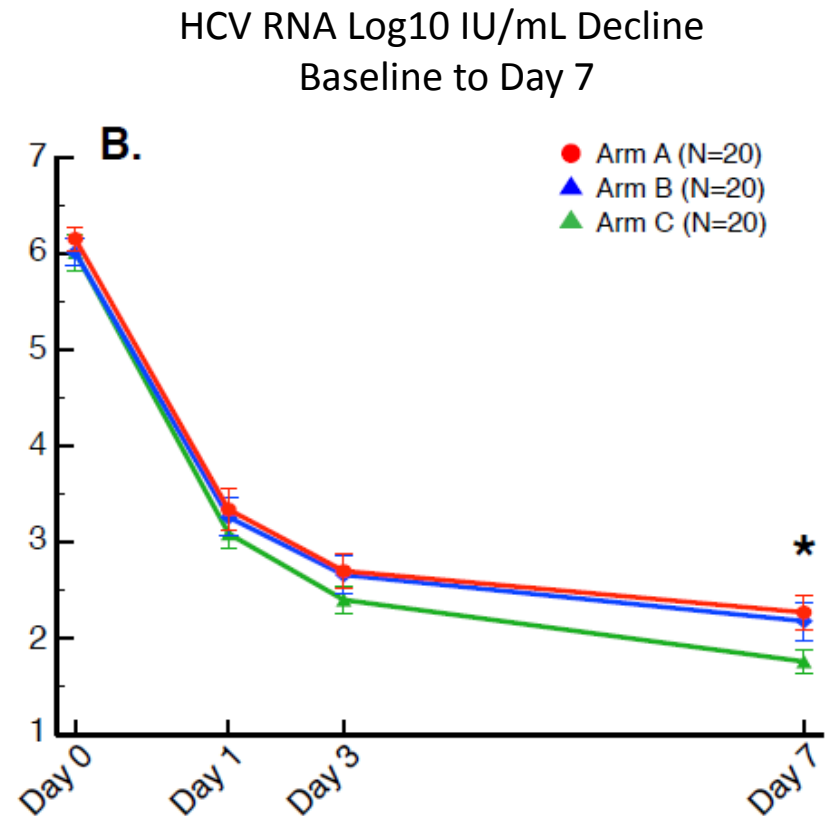
Efficacious in all patient populations

Accessible

1. Hunt and Pcos. *Curr Gastroenterol Rep.* 2013;15:303; 2. Zhou XJ. *Cambridge Healthcare Institute's 15th Annual HCV Drug Discovery*. San Diego, California, April 18-19, 2012; 3. Sulkpowsli et al. http://www.natap.org/2013/APASL/APASL_33.htm. Accessed September 9, 2013; 4. Data on file, Celgene Corporation. 5. Lawitz. *J Hepatol.* 2012;57:24; 6. Nettles et al. *Hepatology.* 2011;54:1956; 7. Wilfret et al. *Antimicrob Agents Chemother.* 2013 Jul 29 [Epub ahead of print]; 8. Pockros. *Expert Opin Biol Ther.* 2011;11:1611.

Sofosbuvir/Ledipasvir FDC alone for 12 weeks or in combination with GS-9451 or GS-9669 for 6 weeks: NIAID SYNERGY

- GS-9451: QD protease inhibitor (80mg)
- Treatment naïve, genotype 1 infected patients
 - African American, 88%
- Virologic response
 - A. SOF/LDV x 12 wks (n=20)
SVR12 100%
 - B. SOF/LDV/9669 x 6 wks (n=20)
SVR4 90%; Relapse, n=1
 - c. SOF/LDV/9451 x 6 wks (n=20)
SVR4 100%
 - No discontinuation or SAE



Case: Man with Cirrhosis and HCV Genotype

3

- 55-year-old man with HCV genotype 3 and compensated cirrhosis
 - He was diagnosed after his former wife died from HCV-related hepatocellular carcinoma
 - Biopsy – METAVIR F4 and moderate steatosis
 - Upper endoscopy – small varices
 - CT scan with contrast – no liver mass
- Treated with PEG-IFN plus RBV 400 mg BID x 24 weeks
 - Response followed by viral relapse
- Treated with PEG-IFN plus RBV 600 mg BID x 48 weeks
 - Response followed by viral relapse

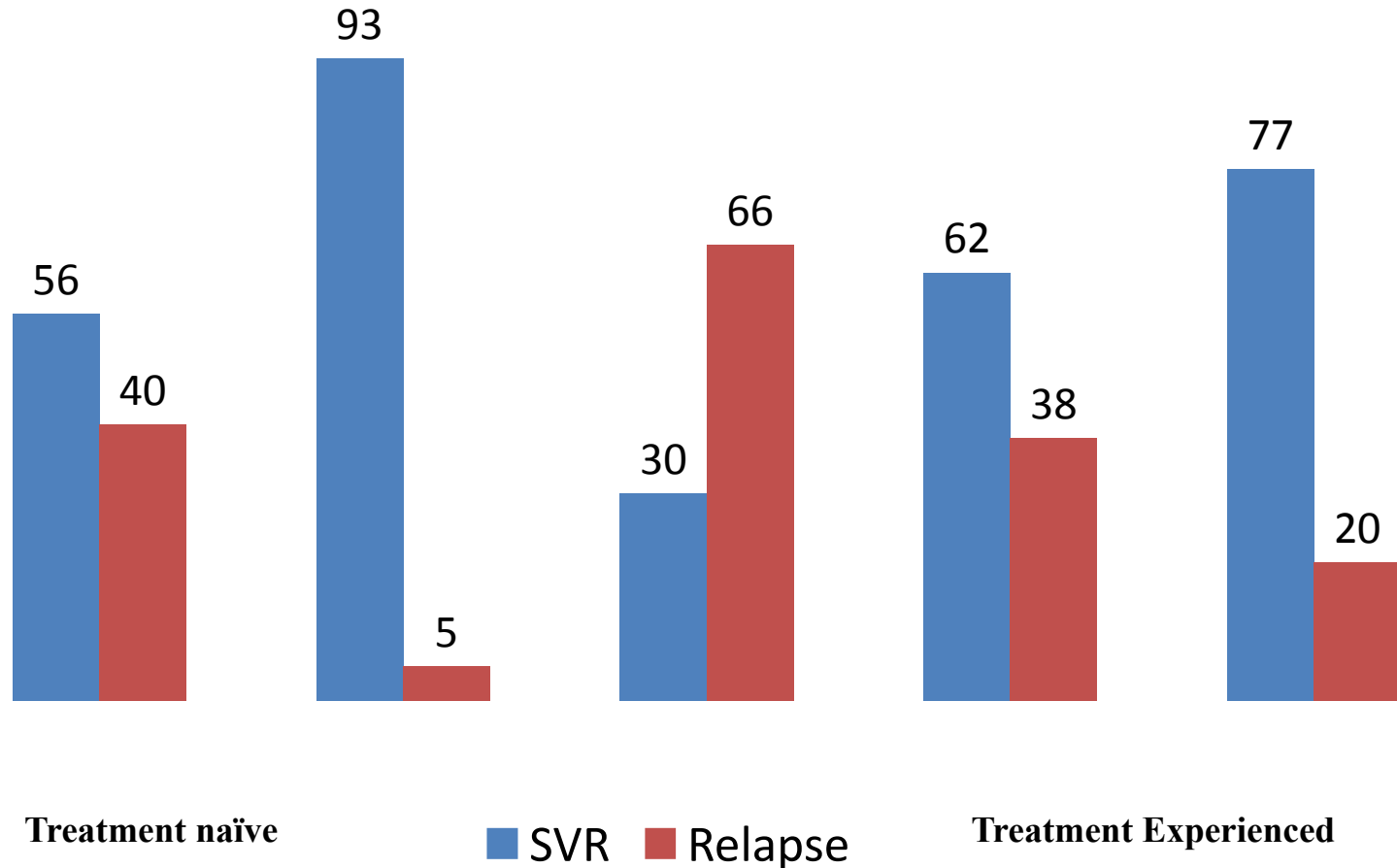
Case Continued:

Man with Cirrhosis and HCV Genotype 3

- He was started in a clinical trial: Treated with Sofosbuvir 400 mg/day + RBV 600 mg BID x 12 weeks
 - Response followed by viral relapse
- What next?
 - Re-treat with SOF + RBV for longer 16 or 24 weeks?
 - Re-treat with SOF + PEG-INF + RBV?
 - Add another DAA — Combination of SOF + daclatasvir
 - or SOF + GS-5816?

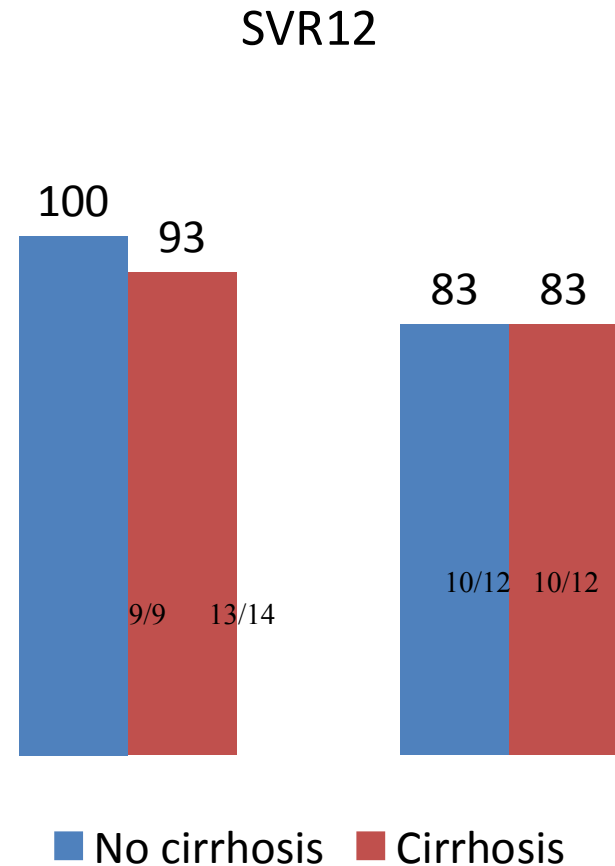
Effect of treatment duration with sofosbuvir plus ribavirin in HCV genotype 3 infected patients

FDA Analysis of FISSION, POSITRON, FUSSION, VALENCE



Sofosbuvir plus PegIFN/RBV for 12 weeks in treatment experienced patients with Genotype 2 or 3: LONESTAR-2

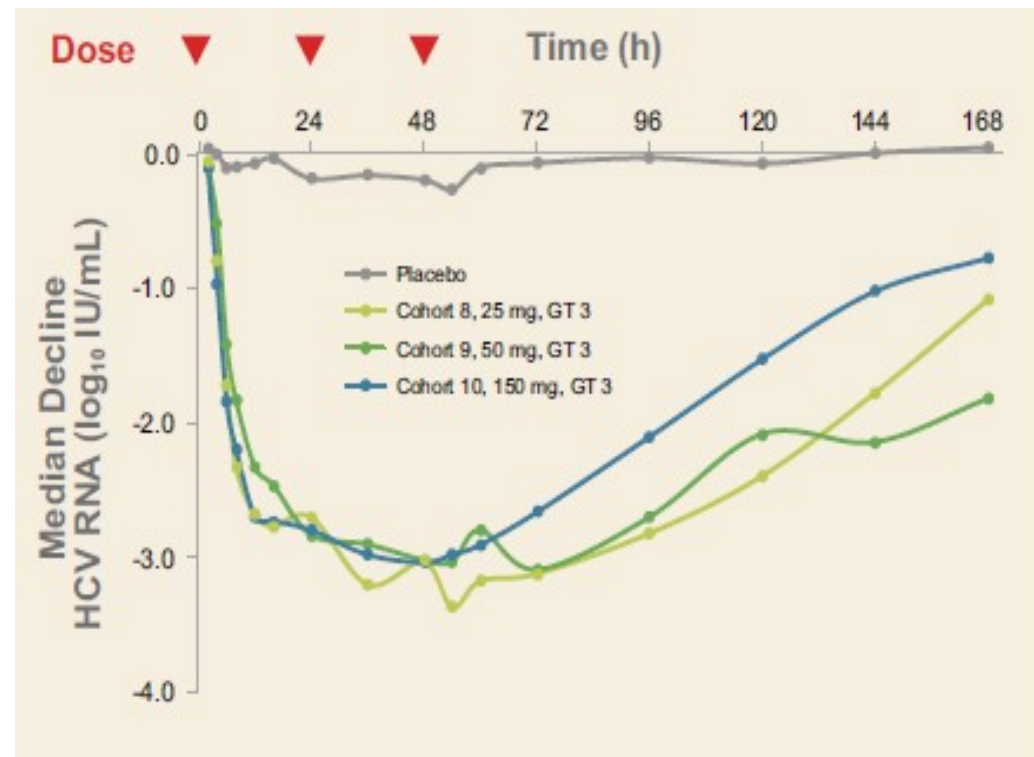
- 47 patients with GT 2 (n=23) or GT 3 (n=24)
 - Cirrhosis, n=26 (55%)
 - Prior relapse, 85%
- Single arm, open label SOF 400 mg QD + PegIFN/RBV for 12 weeks
- Non-SVR patients
 - GT 2: Discontinued with quantifiable HCV RNA, n=1
 - GT 3: Lost to follow-up (n=2)
Relapse, n=2
- AEs were consistent with PegIFN/RBV



GS-5816 monotherapy for 3 days in patients infected with genotype 1, 2, 3, or 4

- NS5A inhibitor with activity against genotype 1 – 6 replicons, *in vitro*
- 87 patients dosed QD with GS-5816 5mg – 150mg or placebo
 - GT 3, n=20
- Clinical trials underway for sofosbuvir + GS-5816 +/- RBV in patients with genotype 1-6*

Median HCV RNA decline from baseline in patients with genotype 3 infection



Case: Recurrent HCV post-transplant and renal insufficiency

- 59-year-old man with HCV genotype 1b s/p liver transplant x 2 with recurrent hepatitis C
 - Renal insufficiency – Cr 1.9
 - Anemia – Hb 10.1
 - Evidence of bridging fibrosis/early cirrhosis
 - He is not a candidate for re-transplantation
- Treated with PegIFN + RBV + Telaprevir
 - Intensive care unit with gram negative bacteremia/sepsis
- Presents to discuss treatment options

Case: Recurrent HCV post-transplant and renal insufficiency

- Sofosbuvir 400 mg/day + RBV 400 mg/day
 - Pre-treatment HCV RNA = 32 million IU/mL
 - HCV RNA < 29 IU/mL by week 6 of treatment
- Hemeoglobin falls to 6.7 g/dL and he develops severe gout in the setting of hyperuricemia
 - Oral prednisone (Steroids)
 - RBV is held
- Add daclatasvir 60 mg/day (compassionate access)
- After 16 weeks of therapy, worsening renal function
 - BUN 86; Cr 6.5 – hemodialysis
 - Candidate for kidney transplant – if HCV is cured