Utility of Hepatitis C Viral Load Monitoring with Ledipasvir and Sofosbuvir Therapy (Poster 689)

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INTRODUCTION

- In October 2014, a combination directly acting antiviral (DAA) regimen consisting of ledipasvir (LDV) and sofosbuvir (SOF) was approved by the Food and Drug Administration for the treatment of chronic HCV genotype 1 infection.
- On treatment hepatitis C (HCV) RNA levels were early predictors of treatment response and the mainstay of response-guided therapy to previous interferon-containing regimens.
- The clinical utility of HCV RNA levels to guide treatment duration and predict treatment outcome with DAA-only therapy needs to be evaluated.

AIM

- To determine the ability of HCV RNA levels at week 4 (W4) and end of treatment (EOT) to predict treatment outcome in HCV patients with or without HIV co-infection treated with LDV/SOF for 12 weeks.

METHODS

Study Design

- 67 HCV genotype 1 patients without cirrhosis or prior treatment experience were enrolled in two NIAID phase 2 trials and treated with a single pill regimen of LDV/SOF (90 mg/400 mg) once daily for 12 weeks:
  - SYNERGY[1]: HCV mono-infected participants without cirrhosis (n=17)
  - ERADICATE[2]: HIV/HCV co-infected participants without cirrhosis – on combination antiretroviral (ARV) therapy (n=37) or ARV naïve (n=13)
- Primary outcome measurement was sustained virologic response (SVR12), defined as HCV RNA below lower limit of quantification (LLOQ) 12 weeks post-treatment.

HCV RNA Measurements

- Serial measurements of HCV RNA levels were taken.

Assay	Assay Result	Abbreviation Used	Definition
Roche COBAS TaqMan HCV Test (LLOQ: 43 IU/mL)	43 IU/mL - 69 million IU/mL	≥LLOQ	Quantifiable
	<43	TD <LLOQ	Unquantifiable but detectable
	None detected	TND <LLOQ	Undetectable
Abbott RealTime HCV Assay (LLOQ: 12 IU/mL)	12 IU/mL - 100 million IU/mL	≥LLOQ	Quantifiable
	<12 detected	TD <LLOQ	Unquantifiable but detectable
	<12 not detected	TND <LLOQ	Undetectable

LLOQ – lower limit of quantification; TD – target detected; TND – target not detected

Calculations

- Negative predictive value (NPV) and positive predictive value (PPV) of HCV RNA at W4 and EOT:

$$\text{NPV} = \frac{\#\text{ patients with HCV RNA } {}^{3}\text{LLOQ or TD<LLOQ who fail treatment}}{\#\text{ patients with HCV RNA } {}^{3}\text{LLOQ or TD<LLOQ who fail treatment}} \text{ or } \frac{\#\text{ patients with HCV RNA } {}^{3}\text{LLOQ who fail treatment}}{\#\text{ patients with HCV RNA } {}^{3}\text{LLOQ who fail treatment}}$$

$$\text{PPV} = \frac{\#\text{ patients with HCV RNA TND<LLOQ who achieve SVR12}}{\#\text{ patients with HCV RNA TND<LLOQ}} \text{ or } \frac{\#\text{ patients with HCV RNA <LLOQ who achieve SVR12}}{\#\text{ patients with HCV RNA <LLOQ}}$$

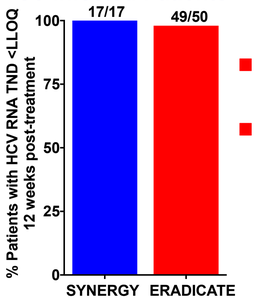
Statistics

- Baseline demographics were compared using t-test for continuous outcomes and Fisher's exact test for binary outcomes (Prism 6.0).

Table 1: Baseline Demographics and Clinical Characteristics of Study Participants

Characteristics	SYNERGY (n=17)	ERADICATE (n=50)	p value
Mean Age ± SD	57 ± 8.5	57 ± 8.1	0.94
Male (%)	11 (65)	37 (74)	0.54
Race (%)			1.00
Black	14 (82)	42 (84)	
White	3 (18)	8 (16)	
Mean BMI ± SD	26 ± 4.1	27 ± 5.3	0.55
HCV Genotype (%)			0.03
1a	8 (47)	39 (78)	
1b	9 (53)	10 (20)	
HCV RNA >800,000 IU/mL (%)	13 (76)	27 (54)	0.15
IL28B Genotype (%)			0.29
CC	5 (29)	8 (16)	
CT/TT	12 (71)	42 (84)	
Fibrosis Score			1.00
0-2	13 (76)	37 (74)	
3	4 (24)	13 (26)	

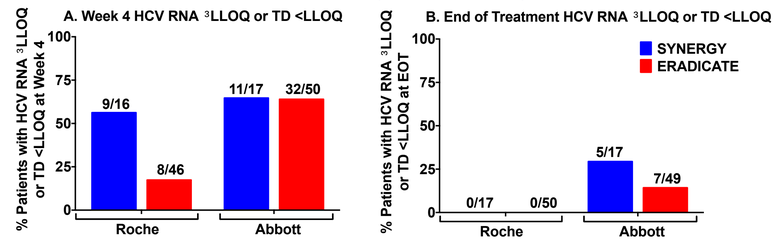
Figure 1: High Rates of SVR12 with LDV/SOF Therapy in HCV Mono-infected and HIV/HCV Co-infected Patients



- SYNERGY: 100% (17/17) of patients achieved SVR12.
- ERADICATE: 98% (49/50) of patients achieved SVR12. The patient who relapsed was on ARV therapy.

RESULTS

Figure 2: Patients with HCV RNA ≥LLOQ or TD <LLOQ at W4 and EOT



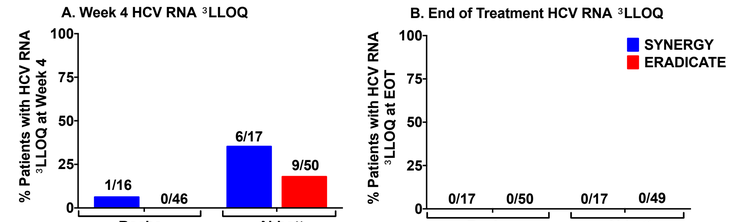
	Roche		Abbott	
NPV	0/9 (0)	1/8 (13)	0/11 (0)	1/32 (3)
PPV	7/7 (100)	38/38 (100)	6/6 (100)	18/18 (100)

	Roche		Abbott	
NPV	-	-	0/5 (0)	0/7 (0)
PPV	17/17 (100)	49/50 (98)	12/12 (100)	42/42 (100)

One patient on SYNERGY and four patients on ERADICATE did not have a Roche assay completed at week 4. The patient who experienced viral relapse on ERADICATE did not have an Abbott assay completed at end of treatment.

- The majority of patients with HCV RNA ≥LLOQ or HCV RNA TD <LLOQ at week 4 achieved SVR12 (NPV <13%).
- 5 patients on SYNERGY and 7 patients on ERADICATE had HCV RNA TD <LLOQ at EOT by the Abbott assay. All 12 patients achieved SVR12. By the Roche assay, all patients had HCV RNA TND <LLOQ at EOT.

Figure 3: Patients with HCV RNA ≥LLOQ at W4 and EOT



	Roche		Abbott	
NPV	0/1 (0)	-	0/6 (0)	1/9 (11)
PPV	15/15 (100)	45/46 (98)	11/11 (100)	41/41 (100)

	Roche		Abbott	
NPV	-	-	-	-
PPV	17/17 (100)	49/50 (98)	17/17 (100)	49/49 (100)

- The majority of patients with HCV RNA ≥LLOQ achieved SVR12 (NPV <11%).
- All patients had HCV RNA <LLOQ at EOT.

CONCLUSIONS

- Low negative predictive values of HCV RNA at week 4 underscore the importance of continued therapy for patients who fail to achieve undetectable levels of HCV RNA early on during treatment because the likelihood of achieving SVR12 is still high.
- Contrary to past experience with interferon-containing treatments, the presence of detectable HCV RNA at EOT is not predictive of relapse in these studies.

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References: 1. Kohli A, et al., "Virological response after 6 week triple-drug regimens for hepatitis C: a proof-of-concept phase 2A cohort study," *Lancet*. 2015.
2. Osinusi A, et al., "Virologic Response Following Ledipasvir/Sofosbuvir Administration in Patients with HCV Genotype 1 and HIV Coinfections," *JAMA*, (in press).