Retreatment of Genotype 1 Hepatitis C Virus with Sofosbuvir, Simeprevir, and Ribavirin Following Treatment Failure with an NS5A-Containing Direct-Acting Antiviral Regimen

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BACKGROUND

- The development of direct acting antivirals (DAAs) has revolutionized the treatment of hepatitis C virus (HCV); drastically improving sustained virologic response (SVR) rates nearing 100% in most genotype (GT) 1 patients.
- Despite these exceptional cure rates, virologic failures still occur, which has been linked to the emergence of resistance mutations.[1-2]
- For those patients that failed treatment with an NS5A inhibitor, current guidelines recommend retreatment regimens employing the results of resistance testing, extending length of treatment, and adding ribavirin (RBV) to selected DAA regimen.[3]
- If NS5A inhibitor resistance associated substitutions (RASs) are detected, and NS3 inhibitor RASs are not, treatment with sofosbuvir (SOF), simeprevir (SIM), and RBV for 24 weeks is recommended.[3]
- Given the relative newness of these agents, there is a paucity of data to support these current guideline recommendations.

OBJECTIVE

- To evaluate the effectiveness of SOF + SIM + RBV for 24 weeks in retreating patients who previously failed HCV treatment containing an NS5A inhibitor.

METHODS

- Single center, observational cohort review of HCV patients that received retreatment with SOF + SIM + RBV for 24 weeks prescribed by the Vanderbilt University Medical Center (VUMC) Hepatology or Liver Transplant Clinic between January 2015 and December 2016 after failing treatment with an NS5A-containing DAA regimen.

Endpoints:

- Primary endpoint: SVR at minimum of 12 weeks following treatment completion.
- Secondary endpoints: viral responses on therapy, adverse events, and treatment discontinuations.

Study Population:

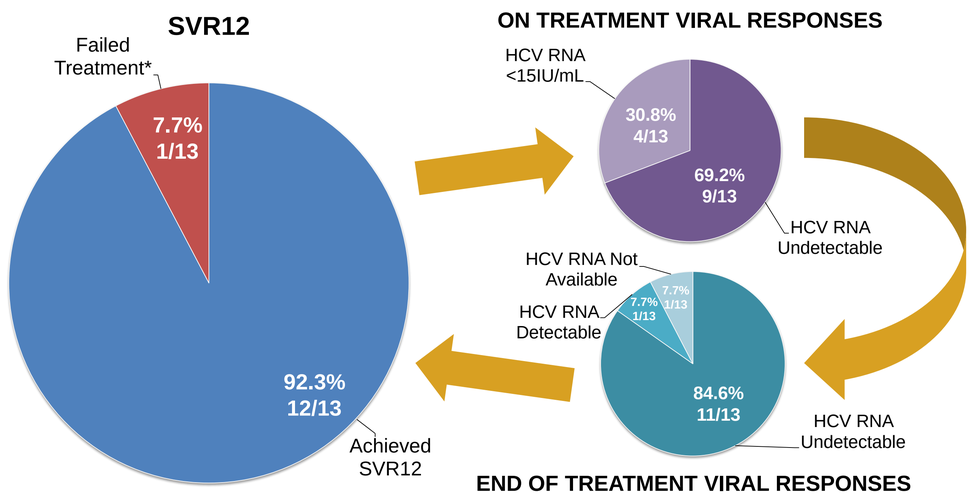
- Inclusion criteria: diagnosis of GT1 chronic hepatitis C, previously failed treatment with an NS5A inhibitor, subsequently prescribed SOF + SIM + RBV for 24 weeks.
- Exclusion criteria: No patients meeting inclusion criteria were excluded from this study.

RESULTS

BASELINE DEMOGRAPHICS (n=13)

Mean age – yr. [range}	53 [23-65]
Male sex – no. [%]	11 [84.6]
Race – no. [%]	
White	10 [76.9]
Black	3 [23.1]
HCV Genotype – no. [%]	
1a	11 [84.6]
1b	2 [15.4]
Mean HCV RNA – log_{10} IU/mL [range]	$3.05x10^6$ [$2.7x10^4$-$2.14x10^7$]
Previous liver transplantation – no. [%]	2 [15.4]
Cirrhosis – no. [%]	8 [61.5]
Child Turcotte Pugh (CTP) score – no. [%]	
CTP A	3 [37.5]
CTP B	5 [62.5]
CTP C	-
MELD score – no. [%]	
<10	9 [69.2]
10-15	4 [30.8]
≥16	-
Previous HCV DAAs received – no. [%]	
NS5A + NS5B*	11 [84.6]
NS5A + NS5B + NS3/4A‡	2 [15.4]

*ledipasvir/sofosbuvir monotherapy
‡ombitasivr, paritaprevir/ritonavir + dasabuvir + ribavirin; simeprevir + sofosbuvir then ledipasvir/sofosbivur



*Demographics of failed patient: prior DAA treatment failure = ombitasivr, paritaprevir/ritonavir + dasabuvir + ribavirin; compensated cirrhosis (CTP A); baseline NS5A RASs = M28T, H58P; baseline NS3 RASs absent

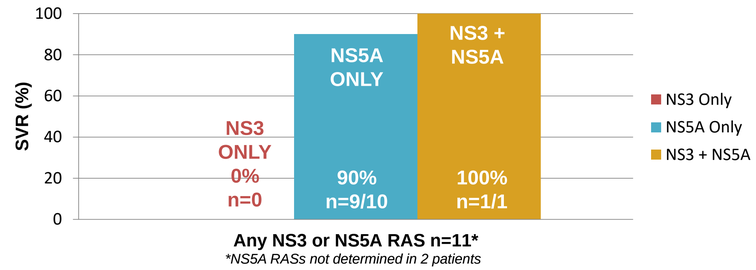
RESULTS

ADVERSE EVENTS (no. [%])

Any adverse event	12 [92.3]
Common adverse events (>10%)	
Fatigue	9 [69.2]
Headache	5 [38.5]
Nausea	4 [30.8]
Emotional Lability	4 [30.8]
Itching/Rash	3 [23.1]
Anemia	3 [23.1]
Insomnia	2 [15.4]
Other *(<10%)	1 [7.7]
Serious adverse events or hospital admission‡	1 [7.7]
Reduction of ribavirin dose due to anemia	4 [30.8]
Discontinuation of treatment owing to any adverse event	**0**

*Sunburn, skin blister, hot flashes, leg cramps, diarrhea, weak, sleepy, disorientation
‡hematemesis/melena –required hospital admission x2 days without intervention; hemoglobin and hematocrit were within normal limits

SVR RATES BY BASELINE RESISTANCE



Any NS3 or NS5A RAS n=11*
**NS5A RASs not determined in 2 patients*

- NS3 RASs Detected = Q80k (n=1)
- NS5A RASs Detected = Q30H/R/Q (n=6); Y93H/C/N (n=5); L31M/L (n=2); M28T(n=1); H58P(n=1)

CONCLUSIONS

- The use of SOF + SIM + RBV for 24 weeks is highly efficacious in patients who previously failed treatment with an NS5A-containing DAA regimen, thus aligning with current guideline recommendations.
- Despite a high prevalence of adverse events, treatment with SOF + SIM + RBV was generally well-tolerated in patients, even those with mildly decompensated cirrhosis (CTP B), resulting in no treatment discontinuations.

References:

1. Sarrazin C, Dvory-Sobol H, Svarovskaia E, et al. 2016. Prevalence of resistance-associated substitutions in HCV NS5A, NS5B, or NS3 and outcomes of treatment with ledipasvir and sofosbuvir. *Gastroenterology*. 151:501-12.
2. Lawitz E, Flamm S, Yang JC, et al. 2015. *Retreatment of patients who failed 8 or 12 weeks of ledipasvir/sofosbuvir-based regimens with ledipasvir/sofosbuvir for 24 weeks*. Presented at Annu. Meet. Eur. Assoc. Stud. Liver (EASL), 50th, Apr. 22-26, Vienna, Austria, Abstr. 0005.
3. American Association for the Study of Liver Diseases and Infectious Diseases Society of America (AASLD-IDSA). 2016. *Recommendations for testing, managing, and treating hepatitis C*. http://www.hcvguidelines.org.