Real-world Impact of Resistance-Associated Substitutions on Retreatment After Ledipasvir/Sofosbuvir Virologic Failure in Hepatitis C Patients

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BACKGROUND

- The US Department of Veterans Affairs (VA) is the largest provider of HCV care in the US and has treated over 113,000 Veterans wth direct acting antivirals
- More than 66,000 Veterans have received treatment with ledipasvir/ sofosbuvir (LDV/SOF)
- Pre-existing polymorphisms or drug resistance-associated substitutions (RAS) have been described in vitro and in clinical trials and are known to be associated with HCV regimen failure
- Understanding the real-world impact of RASs on re-treatment after LDV/SOF virologic failure in HCV-infected patients is necessary for informed treatment decisions

AIM

To evaluate the impact of RASs on SVR in HCV-infected patients retreated after LDV/SOF virologic failure

METHODS

- Observational cohort analysis using the Veterans Affairs Hepatitis C Clinical Case Registry, an extract of the VA electronic medical record
- Inclusion: Genotype (GT) 1a patients who received at least 8 weeks of LDV/SOF by 30 June 2017, failed LDV/SOF treatment, went on to get re-treated with either LDV/SOF or another regimen, and completed retreatment by 31 January 2018
- RAS testing performed after LDV/SOF virologic failure and before retreatment
- RAS testing and retreatment regimen was at the discretion of the provider
- SVR was defined as HCV RNA below the limit of quantification ≥10 weeks after EOT
- Plasma samples were assayed at the VA Public Health Reference Laboratory (Palo Alto, CA USA)
- HCV RNA was extracted from plasma, and then RT-PCR amplified for the NS3, NS5A, and NS5B genes using HCV genotype-specific primers
- Sanger sequencing was performed on amplicons, and sequences were aligned to genotype-specific reference strains using Geneious software, and RASs were called based on publicly available information
- SVR data available through 30 September 2018

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RESULTS

- 439 GT1a patients had RAS testing after LDV/ SOF failure and prior to DAA retreatment
- The most frequent RASs found in each gene are listed in Table 1

Table 1. Summary of RASs Identified, by Gene

	NS3	NS5A	NS5B
Total Tested	234	419	159
# with RASs found	114	326	9
% with RAS	48.7%	77.8%	5.7%
N (%) with NO RASs	120 (51.3%)	93 (22.2%)	150 (94.3%)
RASs Found (n, RAS)			
	NS3	**NS5A***	**NS5B**
	101 Q80K	103 Q30R	3 S282T
	8 R155K	70 L31M	3 S556G
	6 D168E	55 Y93H	1 L159F
	5 T54S	41 Q30H	1 V321A
	5 V55A	38 Y93N	1 E446K
	2 V36M	26 H58P	1 Y448H
	1 V36L	26 Y93C	
	1 V107I	16 M28T	
	1 R155G	15 H58D	
		11 Q30E	
		10 M28V	
		9 K24R	
		8 Q30K; L31V	
		6 Q30L	
		5 M28A	

*Only RASs with 5 or more occurrences are listed

- Key demographics: mean age, 63 years; male, 98%; African American, 44%; FIB-4>3.25, 35%; history of decompensation, 19%
- The three most common re-treatment regimens:
  - ELB/GRZ+SOF+RBV: 100 (23%)
  - VEL/SOF+RBV: 81 (18%)
  - VEL/SOF/VOX: 58 (13%)
- Re-treatment duration:
  - <12 weeks: 7.5%
  - 12 weeks: 48.7%
  - 16 weeks: 14.1%
  - 24 weeks: 26.7%
- The number of people with a documented RAS to the re-treatment regimen prior to initiation was NS3: 5, NS5A: 204, NS5B: 3 (Table 2)

Table 2. Predicted Resistance to Components of Retreatment Regimen

Class	Component	# Receiving	# (%) with RAS to component	RAS(s) Identified
NS3 Inhibitor	Glecaprevir	24	0	
	Grazoprevir	149	4 (3%)	R155K
	Paritaprevir	5	1 (20%)	Q80K
	Simeprevir	49	0	
	Voxilaprevir	60	0	
NS5A Inhibitor	Elbasvir	149	104 (70%)	K24R, Q30H/K/L/R/Y, L31I/M/V, M28A/T/V, Y93C/H/N/S, H58D/P, H45R
	Ledipasvir	58	15 (26%)	L31M, K24R, Q30R, M28A/V, Q30H, Y93H/N
	Ombitasvir	5	1 (20%)	Q30E
	Velpatasvir	154	72 (47%)	Q30E/H/K/L/R/Y, L31I/M/V, H54R, H58D/P, Y93C/H/N/S, K24R, K31M, M28T/V
	Pibrentasvir	24	12 (50%)	H54R, Y93H/N, M28T/V, Q30H/R, H58D, L31M
NS5B Inhibitor	Dasabuvir	5	0	
	Sofosbuvir	373	3 (0.8%)	S282T, L159F, V321A

Table 3. SVR Rates by Regimen for Patients Retreated after LDV/SOF Failure, Based on the Presence of RASs to Any of the Three Genes or Only RASs for NS5A

Retreatment Regimen	SVR in those with **any resistance testing**	SVR in those **without resistance** to the retreatment based on RASs	SVR in those **with resistance** to the retreatment based on RASs	SVR in those with **NS5A resistance testing**	SVR in those **without NS5A resistance** to the NS5A retreatment inhibitor	SVR in those **with NS5A resistance** predicted to the NS5A retreatment inhibitor
Overall	86.1% (372/432)	86.4% (197/228)	85.8% (175/204)	85.9% (354/412)	85.7% (180/210)	86.1% (174/202)
ELB/GRZ	78.6% (11/14)	90.9% (10/11)	33.3% (1/3)	76.9% (10/13)	81.8% (9/11)	50.0% (1/2)
ELB/GRZ+RBV	72.0% (18/25)	**92.9% (13/14)**	**45.5% (5/11)***	75.0% (18/24)	**100% (13/13)**	**45.5% (5/11)***
ELB/GRZ+SOF	100% (10/10)	100% (1/1)	100% (9/9)	100% (10/10)	100% (1/1)	100% (9/9)
ELB/GRZ+SOF+RBV	92.0% (92/100)	100.0% (18/18)	90.2% (74/82)	91.8% (89/97)	100% (15/15)	90.2% (74/82)
GLE/PIB	88.9% (16/18)	88.9% (8/9)	88.9% (8/9)	88.2% (15/17)	87.5%% (7/8)	88.9% (8/9)
GLE/PIB+RBV	80.0% (4/5)	66.7% (2/3)	100.0% (2/2)	80.0% (4/5)	66.7% (2/3)	100.0% (2/2)
LDV/SOF	76.9% (20/26)	76.9% (20/26)	--	76.0% (19/25)	76.0% (19/25)	--
LDV/SOF+RBV	90.3% (28/31)	93.8% (15/16)	86.7% (13/15)	90.3% (28/31)	93.8% (15/16)	86.7% (13/15)
SIM+SOF	92.9% (13/14)	92.3% (12/13)	100.0% (1/1)	92.9% (13/14)	92.9% (13/14)	--
SIM+SOF+RBV	94.1% (32/34)	94.1% (32/34)	--	93.9% (31/33)	93.9% (31/33)	--
VEL/SOF	84.6% (11/13)	90.9% (10/11)	50.0% (1/2)	84.6% (11/13)	90.9% (10/11)	50.0% (1/2)
VEL/SOF+RBV	74.4% (58/78)	69.0% (29/42)	80.6% (29/36)	74.0% (54/73)	67.6% (25/37)	80.6% (29/36)
PrOD+RBV	66.7% (2/3)	66.7% (2/3)	--	50.0% (1/2)	50.0% (1/2)	--
PrOD+SOF+RBV	100.0% (2/2)	100.0% (1/1)	100.0% (1/1)	100.0% (2/2)	100.0% (1/1)	100.0% (1/1)
VEL/SOF/VOX	93.0%% (53/57)	92.3% (24/26)	93.5% (29/31)	92.2% (47/51)	90.0% (18/20)	93.5% (29/31)
VEL/SOF/VOX+RBV	100% (2/2)	--	100% (2/2)	100% (2/2)	--	100% (2/2)

*P<0.05 between those with and without resistance predicted based on RASs

Table 4. SVR by the Presence or Absence of Specific RAS

Gene	RAS	% SVR without RAS	% SVR with RAS
NS3	Q80K	88.0% (117/133)	83.2% (84/101)
NS5A	M28A/G	86.6% (348/402)	60.0% (6/10)
	L31I/M/V	85.8% (284/331)	86.4% (70/81)
	Q30E/G/H/K/R	84.7% (210/248)	87.8% (144/164)
	H58D	86.7% (346/399)	61.5% (8/13)*
	Y93C/H/N/S	86.1% (248/288)	85.5% (106/124)

*P<0.05 between those with and without specified RAS

Table 5. SVR by Number of NS5A RAS

Number of NS5A RASs	% SVR
0	87.6% (92/105)
1	85.8% (194/226)
2+	84.0% (68/81)

CONCLUSIONS

- In this real-world cohort of LDV/SOF virologic failures, NS5A RASs did not substantially affect SVR for most retreatment regimens, although SVR with retreatment were low overall
- SVR rates were numerically lower in patients retreated with LDV/SOF and VEL/SOF±RBV, and significantly lower in patients retreated with ELB/GZR±RBV
- Individual mutations were associated with varying effect on SVR with the NS5A M28A/G and H58D with the largest effect
- Other host or viral factors may be contributing to the less than expected SVR rates
- **Limitations:** baseline samples were not available for comparison of preexisting mutations prior to LDV/SOF treatment with those found after treatment; population sequencing may not have detected mutations present at lower frequency