Ledipasvir/Sofosbuvir HCV Treatment Failures in the Real World: What Patients are at Risk?

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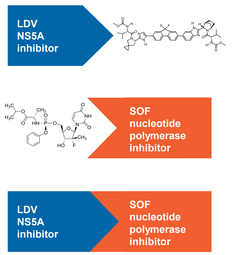
Background

- Ledipasvir/Sofosbuvir (LDV/SOF) fixed dose combination is approved for treatment of hepatitis C virus (HCV) genotypes (GT) 1, 4, 5, and 6. In clinical trials LDV/SOF resulted in sustained virologic response (SVR) rates of 94 to 98% across most patient subgroups.
- Recent studies of real world outcomes report similar SVR rates of 94% to 97%.
- As more patients are treated with this regimen, a population of LDV/SOF treatment failures is emerging.
- Factors associated with virological relapse have been identified in previous studies: ION-1 (nonadherence), ION-4 (Black race, TT allele), TRIO (males, platelets<100,000 per mm^3, cirrhosis, prescribing outside FDA guidelines), HCV-TARGET (proton pump inhibitor use), and Backus et al. (Black race and cirrhosis).



Objective

Describe patient and disease characteristics associated with LDV/SOF failures.

Methods

- This case series includes all adult patients treated at one of seven Mount Sinai Medical Center outpatient clinic locations for chronic hepatitis C, who failed LDV/SOF therapy between November 2014 and January 2016 (n=29).
- This study was Institutional Review Board approved, informed consent was waived.
- Demographic, virological and clinical data were collected through review of electronic medical records, including patient's adherence to therapy. Nonadherence was determined if a patient missed at least one week of therapy.
- Relapse was determined by any detectable virus after completion of therapy. Data were collected through Post Treatment Week 24 visit.
- Diabetes (DM) was determined using the American Diabetes Association guidelines of a hemoglobin A1C >6.5%, a fasting glucose ≥126 mg/dL, or a random glucose reading of >200 mg/dL with symptoms.
- Chronic Kidney Disease (CKD) was defined as a glomerular filtration rate (GFR) <60 mL/min/1.73m^2.
- Liver fibrosis was assessed. Cirrhosis was defined by FibroScan score ≥12.5 kPa, liver biopsy, fibrometer or hepascore. If not available, a FIB-4 score >3.25 was utilized.
- Where applicable, resistance testing was conducted using LabCorp HCV Genosure NS3/4A and NS5A Drug Resistance Assay to identify resistance associated variants (RAVs).
- A convenience sample of patients (n=102) treated with LDV/SOF who achieved SVR 24 was compared to the Case patients to identify factors associated with treatment failure. Statistical analysis of factors previously associated with LDV/SOF failure (male sex, Black race, cirrhosis, platelets<100,000 per mm^3) was conducted using a chi-squared test. HIV positive patients were excluded from this analysis.

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Results

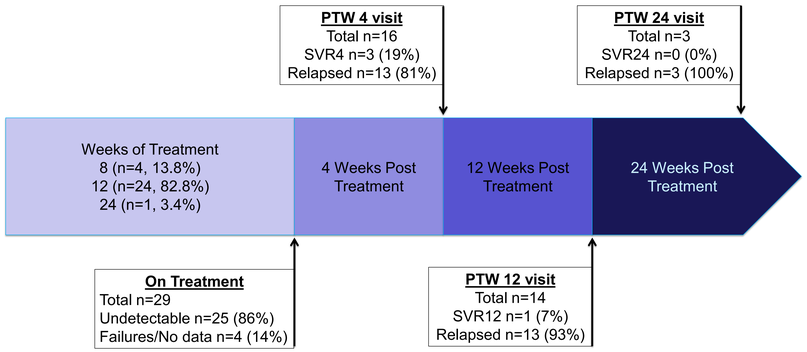
Baseline Patient Demographics and Disease Characteristics

Characteristics	N=29
Age, mean (range) years	59 (34-70)
Male, n (%)	26 (89.7%)
Race, n (%) White Black/African American Hispanic	 4 (13.8%) 17 (58.6%) 8 (27.6%)
Comorbidities, n (%) Diabetes (DM) Hypertension Hyperlipidemia Chronic Kidney Disease (CKD) Liver Transplant (OLT)	 11 (37.9%) 12 (41.4%) 5 (17.2%) 5 (17.2%) 2 (6.9%)
Body Mass Index kg/m^2, mean (range)	27.3 (14.9-44.9)
HIV co-infection, n (%)	7 (24.1%)
Proton Pump Inhibitor (PPI) use, n (%)	8 (27.6%)
HCV Genotype (GT), n (%) GT 1a GT 1b GT 1l GT 6 GT 1 or 4	 18 (62.1%) 8 (27.6%) 1 (3.4%) 1 (3.4%) 1 (3.4%)
HCV RNA, $\log_{10}$ IU/ml, mean (range)	6.62 (4.45-7.64)
History of previous treatment, n (%)	12 (41.4%)
Cirrhosis, n (%) Child Pugh A Child Pugh B	15 (51.7%) 11 4
MELD, mean	13*
History of hepatocellular carcinoma (HCC), n (%)	6 (20.7%)
Lab values, mean (range) Platelets*10^3/mm^3 (ref range, 150-450) Creatinine mg/dL (ref range, 0.7-1.40) Albumin g/dL (ref range, 3.5-4.9) AST U/L (ref range, 1-50) ALT U/L (ref range, 1-53)	 153 (35-300) 1.03 (0.25-2.18)* 3.75 (1.9-4.6)* 74 (25-228) 70 (19-305)

* Data for only 28 patients available

- All HIV patients were well controlled on their antiretroviral (ARV) regimen with undetectable viral load. ARV regimens included ABC/3TC/DTG, TDF/FTC + EFV or DRV/r or RTG or EVG/c or RTG/DRV/r.

Timeline of Post Treatment Follow Up Visits and Relapse Detection



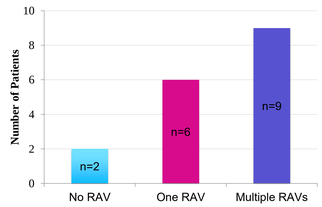
- Patients presented for follow up at variable intervals. Relapses detected by Post Treatment Week (PTW) 4, 12 and 24 are displayed.
- Adherence rates were 79% (n=23).
- 24 patients (82.8%) relapsed by their first PTW visit, and all patients relapsed by PTW 24 visit.

Results (cont.)

Factors Associated with LDV/SOF Treatment Failures in the Reported Literature

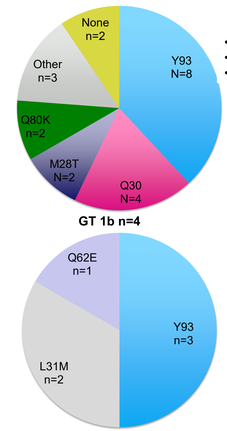
Trial	% Relapse	Reported Factors Associated with Relapse	Mount Sinai OR (95% CI)
ION-1 *(Afdhal NEJM 2014)* n=865	0.3%	Nonadherence	No Data
ION-4 *(Naggie NEJM 2015)* n=335	3%	Black Race	4.96 (1.88-13.09)
TRIO *(Afdhal AASLD 2015)* n=1632	3%	Males Cirrhosis Platelets<100,000/mm^3 Prescribing outside FDA	4.62 (1.28-16.6) 1.62 (0.62-4.19) 1.51 (0.57-3.99) No Data
HCV-TARGET *(Terrault AASLD 2015)* n=781	3%	PPI use	No Data
Backus et al. *(AASLD 2015)* n=3678	9.3%	Cirrhosis Black Race	1.62 (0.62-4.19) 4.96 (1.88-13.09)

Number of RAVs Identified on Post Relapse GT Testing



- 23 patients had repeat GT testing after relapse. All retested for the same GT.
- 58.6% (n=17) had resistance testing performed.

RAVs detected by GT



- Y93 included Y93 C/N/H/Y
- Q30 included Q30 R/H/Q
- Other: L31M/L, E62D, H54Y
- Y93 included Y93 H/Y

Retreatment of Patients Who Failed LDV/SOF

Characteristics	Retreatment Regimen (Duration)			
	SOF/VEL/GS-9857 (12weeks) n=3	SMV/SOF (24 weeks) n=2	OBV/PTV/r+DSV n=1	LDV/SOF+RBV (12 weeks) n=1
Cirrhosis	No	n=1	No	Yes
Previous IFN/RBV	n=2	No	No	No
LDV/SOF Duration	8 weeks (n=1) 12 weeks (n=2)	12 weeks	12 weeks	12 weeks
GT	1a (n=1) 1b (n=2)	1a (n=1) 1b (n=1)	1l	1a
RAVs	Y93H, None, No Data	L31M, Q30R/Y93C	No Data	No Data
SVR	Pending	Pending	Therapy discontinued	Relapsed at PTW4

SMV: Simepravir OBV/PTV/r+DSV: Ombitasvir/Paratapriviir/ritonavir/Dasabuvir

- At the time of this study only 7 patients (24%) had initiated retreatment after LDV/SOF failure. Reasons for delay in retreatment included: awaiting resistance testing results, awaiting drug approval, contraindications to currently available therapies, death and lost to follow up.
- Patients enrolled in POLARIS-1 trial received SOF, Velpatasvir (VEL) a NS5A inhibitor and GS-9857 a NS3/4A protease inhibitor.

Summary and Conclusions

- Clinical trials report high SVR rates with LDV/SOF. These results have been reproduced in the real world setting. However, there is a growing population of patients that have failed LDV/SOF treatment. We describe demographic and disease characteristics of a case series of 29 patients with treatment failure.
- Several risk factors for LDV/SOF failure have been reported in the literature: male sex, Black race, TT allele, cirrhosis, platelets<100,000 per mm^3, PPI use, prescribing outside the FDA guidelines and nonadherence. In our analysis male sex and Black race favored relapse. Cirrhosis and platelets<100,000 per mm^3 were not statistically significant.
- No re-infection was observed. All patients who had repeat GT testing after failure (n=23) retested for the same GT.
- 73% of the patients that had resistance testing had Y93 RAV identified, 53% had multiple RAVs.
- Information about patients who fail treatment may identify groups of patients who would benefit from a longer duration of therapy or a triple-drug regimen.