580: Resistance Associated Variants: Data from the NIAID SYNERGY Trial

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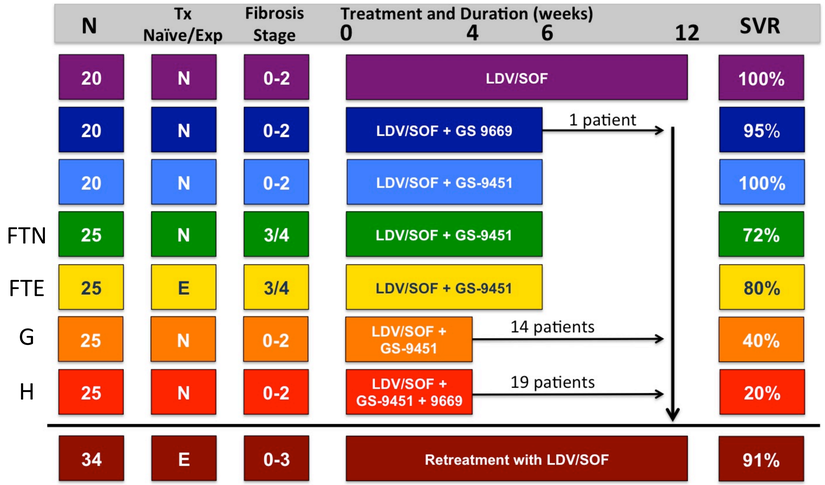
Background

Treatment of chronic hepatitis C (HCV) has rapidly evolved from modestly-effective interferon-based regimens to highly effective, all oral, interferon-free directly acting antiviral (DAA) therapy. While DAAs are used for treatment of HCV worldwide, the impact of emerging resistance is largely unknown. In this study, we evaluated the role of baseline, treatment-emergent and treatment-enriched resistance associated variants (RAVs) of HCV on sustained virologic response (SVR).

Methodology

NIAID SYNERGY is an 8 arm clinical trial that treated over 200 hepatitis C patients with varying ledipasvir (LDV) and sofosbuvir(SOF)-based DAA regimens (Figure 1). Deep sequencing was performed on plasma at baseline from patients in SYERGY arms F, G, or H, at the time of relapse in patients failing therapy, and prior to retreatment, when appropriate.

Figure 1: SYNERGY Study Schema



RAVS were interpreted as shown in Table 1 and classified as baseline, treatment-enriched (those increasing in proportion to wild type from baseline to relapse) and treatment-emergent (those which were not present at baseline). Chi Squared and Fisher's Exact Test were performed to compare response rates for patients with and without RAVs.

Table 1: RAV interpretation by genotype

Fold-Change	Genotype 1a				Genotype 1b	
NS3, Position	Q80K	R155K			Q80L	D168
GS-9451[1,2,3]	3-5 x	>100 x			3-5 x	>100 x
NS5A, Position	M28T	Q30R	L31M/V	Y93H/N	L31V	Y93H/N
Ledipasvir[1,4]	20 x	> 100 x	> 100 x	> 1000 x	?	> 1000 x/?
Fold-Change	**Genotype 1**					
NS5B, Position	S282T	V321I				
Sofosbuvir[1]	?	?				

> 100 x 5 to 100 x < 5 x unknown

1. Lontok, et al Hepatology 2015;62(5).
2. Kattakuzhy, et al CID 2016; 62(4)
3. Dvory-Sobol, et al Antimicrobial Agents and Chemotherapy 2012;56(10)
4. Cheng G, et al. EASL 2012. Abstract 1172.

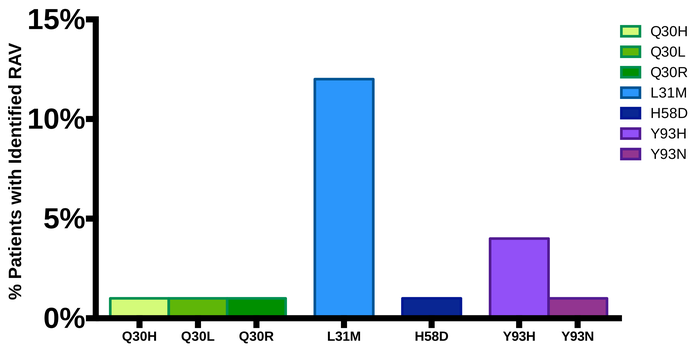
Results

Of 160 patients treated initially, 99 patients had baseline RAV testing available. Prevalence of baseline RAVs and treatment outcomes for these patients are shown in Table 2. For patients receiving at least 6 weeks of therapy, even those with advanced fibrosis, regardless of previous treatment experience, pre-treatment RAVs did not predict SVR (SYNERGY FTN, P=0.063 and P=1.00 for NS3 and NS5A respectively; SYNERGY FTE, P=0.62 and P=0.25). For patients receiving ultra short duration therapy (4 weeks), high level NS5A RAVs (conferring > 100 fold resistance) present prior to treatment were associated with relapse in pooled analysis (SYNERGY G/H, P=0.021). The prevalence and composition of NS5A RAVs at baseline is shown in Figure 2.

Table 2: Baseline RAV Prevalence and Outcome, By Study Arm

	SVR		NS3	NS5A	NS5B
FTN	72%	Prevalence	8/25 32%	3/25 12%	-
		SVR	5/8 63%	2/3 67%	
FTE	80%	Prevalence	11/25 44%	5/25 20%	-
		SVR	10/11 91%	3/5 60%	
G	40%	Prevalence	8/25 33%	2/25 8%	-
		SVR	4/8 50%	0/2 0%	
H	20%	Prevalence	5/24 21%	6/24 25%	1/24 (4%)
		SVR	0/5 0%	0/6 0%	1/1 (100%)

Figure 2: Frequency of Baseline RAVs in All Patients (N=99)



NS5A RAVs emerging after failure of short course therapy were maintained over a median of 24 weeks prior to retreatment (Figure 3). However, when these relapsed patients were retreated with SOF and LDV, 91% achieved SVR in an Intention to Treat (ITT) analysis (Figure 4). Of the 33 patients retreated, 85% (29/34) had high level NS5A resistance (29>25 fold, 28>100 fold), and 89.7% (26/29) achieved SVR_{12} by ITT.

Figure 3: Composition of NS5A RAVs in Relapsed Patients

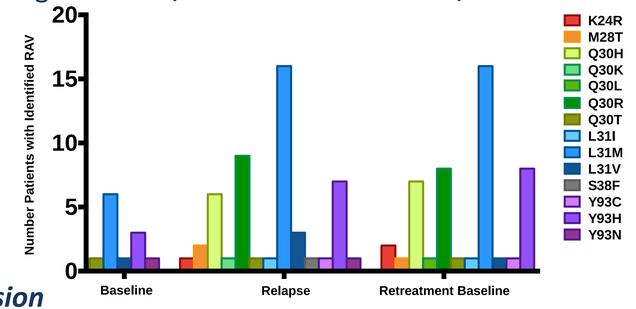
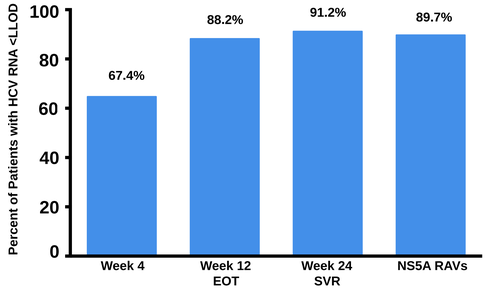


Figure 4: Retreatment of Relapsed Patients



Conclusion

HCV NS5A RAVs do not predict relapse when using sofosbuvir-based treatment for at least 6 weeks or during re-treatment with standard 12 week regimens of LDV/SOF. NS5A RAVs do appear to impact treatment response when treating with ultra-short, 4 week duration therapies.