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HCV Treatment Failure in a Patient Infected with HIV

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Abstract

The treatment of HIV/ Hepatitis C co-infection presents many treatment challenges as newer combination therapies are used. We present a case of Hepatitis C treatment failure in an HIV-coinfected patient which resulted in NS5A, NS5B, and protease (NS4A/NS3) resistance. A 62-year old AA male diagnosed with HIV in 2010 was treated with efavirenz/emtricitabine/tenofovir disoproxil fumarate with complete virologic suppression for 5 years and CD4 >300. He was co-infected with Hepatitis C Genotype 1a with pretreatment HCV RNA of 7.6 log (44,000,000 copies/ml) and baseline HCV RNA of 6.9 log (8,300,000 copies/ml). A liver ultrasound and serum AFB was unremarkable.A 2011 liver biopsy showed minimal chronic hepatitis with no significant fibrosis (histologic stage and grade: Grade 1/4, Stage 0/4). A Prometheus® FIBROSpect ® II completed immediately prior to treatment resulted in a FIBROSpect II Index score of 38. (consistent with a Metavir score of F0-F1). Ten days prior to the start of ombitasvir/paritaprevir/ritonavir/ dasabuvir (PrOD) and weight-based ribavirin(RBV), his HIV regimen was switched to dolutegravir and emtricitabine/tenofovir disoproxil fumarate(FTC/TDF). He was subsequently initiated on PrOD plus RBV and serial HCV RNA and HIV viral loads were obtained (See Table). Concurrent medications were daily HCTZ and monthly intramuscular testosterone. HCV treatment was discontinued at week 10 and HCV resistance testing was performed and showed pan resistance to NS5A (Y93H), NS5B (C316C/Y), NS3/NS4A(F43L, Q80K, I132L/V, D168E). During HCV treatment, the patient communicated complete adherence to HCV and HIV treatments. Additionally, he had received home nursing visits, had extensive counseling and review of OTC medications and prescriptions for drug-drug interactions, yet failed to achieve an undetectable HCV RNA. Drug-drug interactions among medications used to concurrently treat HIV and HCV are numerous. Efavirenz is a cytochrome P450 enzyme inducer (induction may last for weeks after discontinuation of offending agent) that decreases concentrations of other HCV treatments (ex. simepravir); however, this interaction has not currently been documented between efavirenz and HCV agents in PrOD. No significant interactions have been documented among PrOD, dolutegravir and FTC/TDF. The reasons for treatment failure in this case are unclear.

Background

Resistance associated variants (RAV) occur in chronic Hepatitis C infection at low frequencies (<3%) in treatment naïve patients, with the exception of Q80K which occurs in >10% of HCV Genotype 1a infected patients. While RAV can be demonstrated in the majority of patients with treatment failures while on direct acting antivirals (DAA), the majority of these mutants disappear within 2 years due to poor replication fitness. In a significant number of patients, however, RAV may remain for an extended period of time. In the initial clinical trials of bocepravir, cross-resistant HCV NS3/4A protease inhibitor substitutions associated with treatment failure persisted for 25% of patients at 2.5 years follow up. Currently available highly potent DAA such as the NS5B inhibitor sofosbuvir appear to have a high genetic barrier to resistance. Thus, the current recommendations from the AASLD/IDSA do not recommend RAV testing prior to HCV therapy with highly potent DAA combination regimens for HCV genotype 1a unless grazoprevir and elbasvir are used and also state that lack of RAV testing results or lack of access to RAV testing should not be used as a means to limit access to HCV therapy. We present a case of a patient co-infected with HIV/HCV who developed pan-resistance to all available classes of DAA while on DAA /ART therapy and experienced transient HIV viremia. The mechanism of HCV treatment failure in this co-infected patient remains unknown.

Results

Table 1: HCV and HIV viral loads

Week	HCV RNA (log;copies/ml)	HIV Viral Load (copies/ml)
0	6.9 log; 8,300,000	Detected < 40
4	5.4 log; 230,000	141
7	5.0 log; 110,000	168
10	5.2 log; 150,000	Detected < 40

	Drug		HCV GenoSure®		Assessment	Comments
	Generic Name	Brand Name	Region	Drug Resistance Associated Mutations Detected	Drug	
NI	Sofosbuvir	sofosbuvir	NS5B	None	SOF	Sensitive
NNI	Dasabuvir	dasabuvir	NS5B	C316C/Y	DSV	Resistant

Results (cont.)

	Drug		HCV GenoSure®		Assessment	Comments
	Generic Name	Brand Name	Region	Drug Resistance Associated Mutations Detected	Drug	
NS5AI	Ledipasvir	ledipasvir	NS5A	Y93H	LDV	Resistant
	Ombitasvir	ombitasvir	NS5A	Y93H	OBV	Resistant

	Drug		HCV GenoSure® NS3/4A		Assessment	Comments
	Generic Name	Brand Name	Region	Drug Resistance Associated Mutations Detected	Drug	
PI	Boceprevir	Victrelis	NS3	I132L/V	BOC	Resistance Possible
			NS4A	None		
	Paritaprevir	paritaprevir	NS4A	None	PTV/r	Resistant
			NS3	F43L, Q80K, I132L/V, D168E		
	Simeprevir	Olysio	NS3	F43L, Q80K, D168E	SMV	Resistant
			NS4A	None		
	Telaprevir	Incivek	NS3	I132L/V	TVR	Resistant
			NS4A	None		

Conclusions

Conclusion: Currently, the AASLD/IDSA guidelines do not routinely recommend resistance testing prior to treatment of HCV genotype 1a unless grazoprevir and elbasvir are used or if the patient experiences treatment failure while receiving highly potent DAA combination regimens. Despite attention to known risk factors associated with treatment failure – such as drug/drug interactions, non-adherence, or cirrhosis – this patient experienced transient HIV viremia after 5 years of consistent virologic suppression and was found to have NS5A, NS5B, NS3/NS4A RAV after failure to achieve an undetectable HCV viral load. HCV/HIV treatment is rapidly evolving but remains in the early stages of development. RAV testing prior to initiation of highly potent DAA in HIV/HCV co-infected patients should be considered. Analysis of archived blood samples for the presence of RAV both pre-treatment and at time of testing for the first and second HCV RNA assays are planned.

References

http://www.hcvguidelines.org/