VERY LATE RELAPSE OF CHRONIC HEPATITIS C TREATED WITH LDV/SOF

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Background

Two years after cure with LDV/SOF (09/2015-03/2016, SVR12 06/2016), a 56-year-old patient with history of IVDU and compensated cirrhosis due to chronic hepatitis C (genotype 1b) diagnosed in 2013 presented with viral resurgence (HCV RNA 1.5 x10^5 IU/ml) in 06/2018. HCV RNA had been undetectable on three distinct occasions in the meantime (09/2016, 05/2017 and 02/2018). The patient under stable opioid-substitution without IV drug-use for >15 years and excellent adherence to previous therapy denied any risk behavior for reinfection. Previously he had been fully informed about possible ways of HCV-infection. He even volunteered to become a treatment peer in our center. As relevant co-morbidity he has an insulin-dependent diabetes mellitus.

The patient already had experienced viral relapse in 02/2015 (HCV RNA 0.3 x10^5 IU/ml) after HCV-therapy with peginterferon and ribavirin plus boceprevir (08 respectively 09/2013-07/2014) with ETR but no SVR12-value documented.

Methods

NS3, NS5A and NS5B sequences from plasma samples collected prior to treatment and following relapse were amplified with PCR and sequenced by next-generation sequencing. Consensus sequences of each time-point were compared to determine the percentage of homology and appearance of resistance-associated substitutions (RAS). The sequences were compared to the genetic database of the French National Reference Center for Hepatitis containing >200 genotype 1b sequences.

Extensive inquiries about reinfection from human beings or environmental sources were carried out. We also considered autoinfection with possible unsafe techniques with regards to his Insulin dependent diabetes mellitus and reinfection from the previous index partner.

Results

NS5B sequences from 2015 and 2018 showed a sequence homology of 99.6%, suggesting viral relapse. There was 100% homology between the 2015 and the 2013 isolate supporting a relapse after the first HCV-therapy. A Y93H RAS in NS5A appeared in 2018, present in 99.5% of the viral population, but was not detectable in 2015 prior to treatment (minority cut-off 1%). Phylogenetic analysis of the NS5B region demonstrated a 99% bootstrap value between the samples pointing towards HCV relapse.

No auto-reinfection could be discovered as the patient only used disposable materials for insulin-injection. The ex-girlfriend and probable index case had been cured from hepatitis C several years ago.

Figure 1:

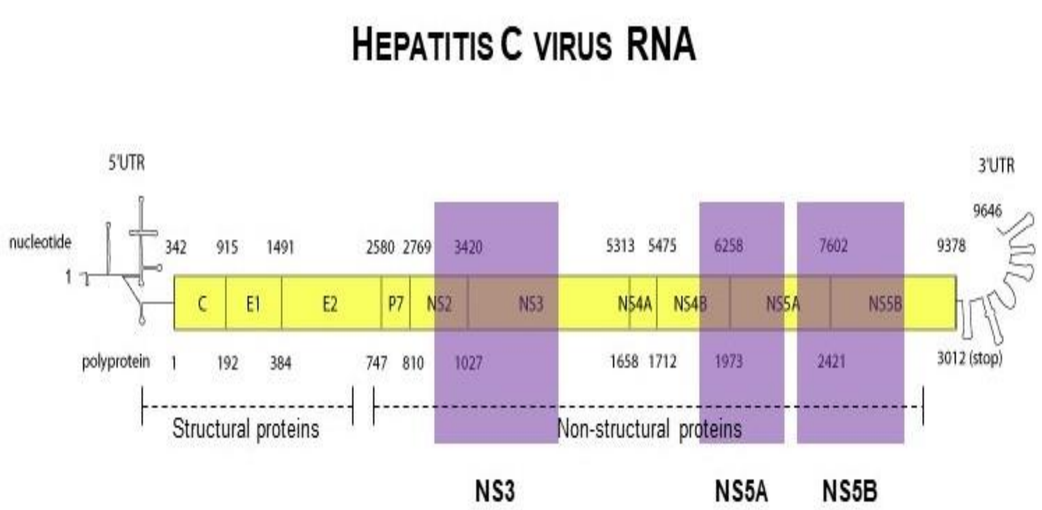


Table 1:

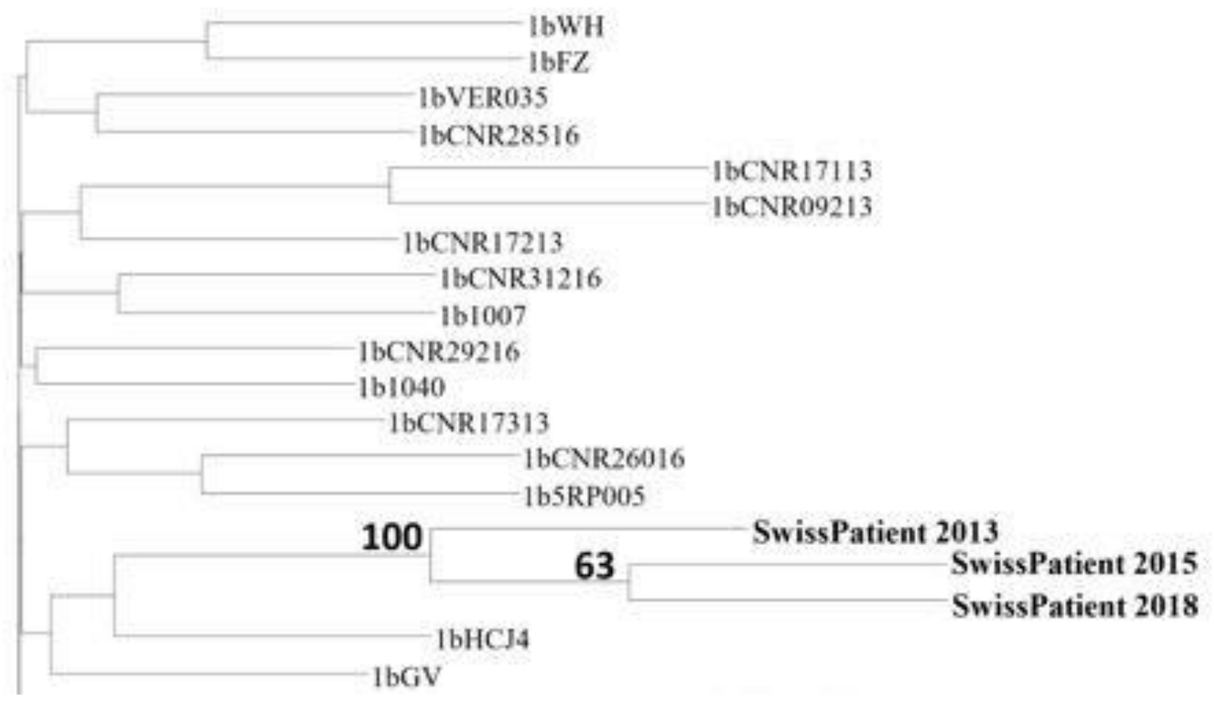
Next-generation sequencing of HCV-positive plasma samples from 2013, 2015 and 2018

Sample	HCV load (log_{10} IU/mL)	Parameters	Protease (NS3)	NS5A	Polymerase (NS5B)
HCV 2013	5.8	Genotype	1b	1b	1b
		Detected SNPs	nd	L28M, Q30R	nd
HCV 2015	4.5	Homology with HCV 2013	NA	NA	100%
		Homology with HCV 2018	NA	NA	99.6%
		Genotype	NA	NA	1b
		Detected SNPs	NA	NA	nd
HCV 2018	5.2	Homology with HCV 2013	99.3%	96.1%	99.2%
		Genotype	1b	1b	1b
		Detected SNPs	nd	L28M, Q30R Y93H	nd

nd= SNPs not detected
NA= results not available; sequencing failed

Figure 2:

Extract of the phylogenetic tree of the patient-NS5B sequences with reference HCV strains of different genotypes and subtypes



Conclusions

Next-generation sequencing and phylogenetic analyses suggest HCV relapse with a Y93H RAS selected by the previous treatment with LDV/SOF. In accordance with this finding thorough inquiries did not detect any source of reinfection.

The published incidence of late relapse after SOF-containing DAA-based therapy is very low (<0.5%). The majority of relapse occurred before 24 weeks post-treatment, making this case with >92 weeks post-treatment even more exceptional.

Relapse following LDV/SOF-treatment was the second event after relapse of first generation NS3/4A-protease inhibitor (boceprevir) based combination therapy 3 years ago that was certainly less exceptional. Yet, it might indicate a particularly difficult to treat virus.

Treatment with GLE/PIB plus SOF plus RBV for a duration of 6 months was started in March 2019. At the date of poster submission the patient concluded 21 weeks of treatment with viral suppression (HCV RNA < 12 IU/ml) since week 4 of treatment.

Limitations

Our study has some limitations: PCR amplification of HCV NS3 and NS5A targets did not yield an amplification product for the plasma sample from 2015 with low HCV RNA viral load. Therefore only HCV NS5B sequences from 2013, 2015 and 2018 could be compared and used for phylogenetic analysis.

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