

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 1.5×10^5 IU/ml). Undetectable HCV RNA loads < 12 IU/ml had been documented 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 did not show any risk behavior for reinfection.

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. Extensive inquiries about possible reinfection were carried out.

Results: NS5B sequences from 2015 and 2018 showed a sequence homology of 99.6%, suggesting viral relapse. 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 supporting HCV relapse. No source of reinfection with the same virus could be identified.

Conclusion: We show HCV relapse with a Y93H RAS selected by the previous treatment with LDV/SOF. 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 >90 weeks post-treatment even more exceptional. Genetic analyses investigating viral resurgence should be encouraged. Treatment with GLE/PIB plus SOF plus RBV for a duration of 6 months was started in March 2019.