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Commentary

Silent damage? Occult HCV replication and histological disease may occur following apparent HCV clearance

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Hepatitis C virus (HCV) infection is a significant source of global morbidity and mortality, with an estimated 3% of all persons infected worldwide and an economic burden in the hundreds of billions [1,2]. However, with the relatively recent introduction of robust and more cost-effective direct acting antivirals (DAA) the World Health Assembly has backed a global HCV elimination strategy by 2030 [1]. This approach will target both chronic HCV-infected patients and those previously undiagnosed and asymptomatic.

With the new DAA combinations, sustained virological response (SVR), which is defined as undetectable HCV RNA at 12 weeks (SVR12) or 24 weeks (SVR24) in serum post treatment completion, has reached 95–100% for certain HCV genotypes and has changed the landscape for hepatic pathology including normalization of liver enzymes, as well as improvement of liver necroinflammation and fibrosis. Nonetheless, several concerns including occult HCV infections, re-infections and resistant/persistent infections in association with DAA therapy remain unsolved. Indeed, in the current era of DAA therapy, how can we determine if 'cured' patients have in fact eliminated all virus systemically? And even if so, are the risks associated with liver injury and hepatocellular carcinoma completely eliminated after SVR? Most studies have shown the presence of HCV RNA in liver and/or PBMC in transplant patients with no viremia indicating incidence of occult infections [3]. Due to limited availability of liver biopsies in non-transplant patients, the clinical significance of these occult HCV infections and their impact on hepatic and extra-hepatic complications have been less well studied in immunocompentent patients post-SVR. A new study by Wang et al. [4] assesses the prevalence of occult HCV infection (OCI) in liver and PBMC of patients following SVR24 achieved with DAA and pegylated ribavarin (PR) treatments and in naturally resolving infections. HCV RNA was observed in approximately 11% of patients by in-situ detection of HCV RNA, namely RNAscope assay of liver biopsies either following DAA and PR at SVR24 or after spontaneous resolution. Further, of the 16 total OCI patients, HCV prevalence was higher in the DAA-treated group and one patient in the PR group relapsed at 48 weeks post treatment, suggesting that a complete 'cure' may be less likely. Almost all patients with intrahepatic HCV RNA (12/13; 92.3%) also tested positive for HCV RNA in PBMC. These data are particularly relevant since it suggests PBMC monitoring could be ideal for detection of OCI for longitudinal follow-up post treatment whereas liver biopsies could be tested based on a case by case basis following negative virus detection in PBMC. A much larger sample size study is necessary to truly determine if PBMC viral loads correlate with liver viral loads.

Wang and colleagues [4] also showed that protracted hepatic inflammation and severe fibrosis score after SVR was associated with OCI compared to fibrosis regression in non OCI patients. The presence of residual RNA/ongoing viral replication in the liver leads to continuous liver injury and does not improve clinical outcomes following HCV clearance. The hepatic alterations in OCI are of serious concern, especially if left unmonitored post-treatment. Since OCI is not always associated with abnormal transaminases, baseline viral loads and treatment regimens, it is imperative to identify biomarkers for diagnosis/prediction of OCI even in the absence of liver biopsy samples. OCI occurred most frequently in patients with genotype 3, which may give some clues as to needed surveillance. However, this could present another difficulty in that genotype 3 primarily circulates in India and Southeast Asia [2], where any biopsy sampling may be logistically more challenging. This also highlights another potential caveat of the study that in addition to small sample size, all the patients were ethnically Chinese. Whether these findings can be fully extrapolated to larger numbers of individuals in the global epidemic will need to be determined.

Overall, the study by Wang et al. [4] has underscored the clinical relevance of OCI and the importance of longitudinal monitoring of patients after SVR and DAA. In addition, it is important to highlight that these findings were seemingly not associated with re-infections which generally result in a similar occult replication and serum clearance, although multiple studies suggest re-infection after SVR and DAA are possible and could mimic these occult pathologies [5]. Future studies with larger cohorts are essential to determine the full etiology of all OCIs and how individuals with these manifestations can be more readily identified and treated without the need for liver biopsies (i.e., biomarkers). It is not currently known what duration of longitudinal monitoring is necessary and if further treatment could be helpful for OCI patients. Therefore, a suitable strategy for not only identification, but also follow-up and treatment of OCI patients will need to be developed to address

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what could be a largely under-appreciated problem in patients who have only seemingly cleared HCV.

Declaration of Competing Interest

The authors declared no conflicts of interest.

References

[1] Tordrup D, Hutin Y, Stenberg K, et al. Additional resource needs for viral hepatitis elimination through universal health coverage: projections in 67 low-income and middle-income countries, 2016-30. Lancet Glob Health 2019;7(9):e1180–8.

[2] Polaris Observatory HCVC. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol 2017;2(3):161–76.

[3] Elmasry S, Wadhwa S, Bang BR, et al. Detection of occult hepatitis C virus infection in patients who achieved a sustained Virologic response to direct-acting antiviral agents for recurrent infection after liver transplantation. Gastroenterology 2017;152(3):550–3 e8.

[4] Wang Y, Rao H, Chi X, et al. Detection of residual HCV-RNA in patients who have achieved sustained virological response is associated with persistent histological abnormality. EBioMedicine 2019. https://doi.org/10.1016/j.ebiom.2019.07.043.

[5] Osburn WO, Fisher BE, Dowd KA, et al. Spontaneous control of primary hepatitis C virus infection and immunity against persistent reinfection. Gastroenterology 2010;138(1):315–24.