The Emergence of New Viral Strains Following Treatment Failure in an HIV-Positive Cohort Infected with Acute HCV

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More than 1000 cases of acute hepatitis C (HCV) in HIV-positive men-who-have-sex-with-men (MSM) have been reported in urban centres in the Europe, Australia and the USA.¹ ² ³

Following treatment, sustained virological response rates (SVR) in acutely HIV/HCV co-infected patients are lower than in acutely HCV mono-infected individuals (59 versus 98%),¹ ⁴ but the reasons for this are not understood.

In HCV-infected patients, the virus circulates as a mixture of closely related but distinct genomes called quasispecies. We studied the dynamics of quasispecies in pre- and post-treatment samples taken from patients who failed standard of care therapy (48 weeks of pegylated interferon alpha and ribavirin) in a chronic HIV/acute HCV cohort of 160 patients.³

Methods

A group of 16 patients failed to respond to treatment. A 220 bp region of the E2 envelope gene including the hypervariable region 1 (HVR-1) (Fig 3) was amplified using nested RT-PCR using a combination of genotype-specific fusion primers. (Fig 2)

PCR products were sequenced by direct sequencing (DS), clonal analysis (CA) and next generation sequencing using a pyrosequencing approach (NGS). Phylogenetic trees were constructed using the maximum likelihood (ML) method.

Using DS, in the 16 patients that failed treatment (six relapers, six null responders and four partial responders), 60% of patients had evidence of a “new variant” post-treatment. However, CA and NGS results revealed that 66% of such “new variants” were present in pre-treatment samples, representing new dominance of a pre-existing minority strain that was not detected by DS. Only two patients had completely new strains, which were presumed to represent re-infection. (Table 1, Fig 3, Fig 4)

NGS was superior to CA in detecting the dominance of pre-existing minority strains in 25% of patients. Both techniques detected multiple strains in 50% of patients that were missed by routine diagnostic methods (DS).

Conclusion

In HCV treatment failure, the emergence of new viral strains may most commonly be attributed to new dominance of pre-existing minority variants rather than re-infection.

References