

Treatment of a patient with genotype 7 HCV infection with sofosbuvir and velpatasvir

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Introduction

During a phase 3 study evaluating the combination of sofosbuvir-velpatasvir for 12 weeks in patients with genotype 1, 2, 4, 5, and 6 HCV infection, we enrolled a patient who was subsequently found to be infected with genotype 7 HCV. This patient tolerated the study regimen well, and achieved sustained virologic response 12 weeks after treatment.

Case Report

In 2012, a 44-year-old male from the Democratic Republic of Congo was referred to the Liver Unit of the Hôpital Erasme in Brussels, Belgium for treatment of hepatitis C virus (HCV) infection. The patient's HCV infection had been discovered during a workup for hypogonadism in another hospital. The route of his HCV infection is unknown. The patient had normal liver enzymes and non-invasive testing excluded significant liver fibrosis (Fibroscan score of 4.7 kPa and FIB-4 score of 0.81). A liver ultrasound returned normal results. The patient's viral load was 3,214,573 IU/mL and the Abbott RealTime HCV Genotype II assay indicated that the patient was infected with genotype 2 HCV. Due to the absence of significant fibrosis, treatment with peginterferon plus ribavirin was not initiated at that time. During annual follow-up appointments, the patient's Fibroscan values remained stable.

In October 2015 the patient was screened for participation in the phase 3 ASTRAL-1 clinical study, a randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of a fixed-dose combination of sofosbuvir-velpatasvir for 12 weeks in patients with genotype 1, 2, 4, 5, and 6 HCV infection (NCT02201940). The patient was initially determined to have genotype 2 infection by the TRUGENE assay (analysis of HCV genotype using the VERSANT HCV Genotype INNO-LiPA 2.0 assay (Siemens) was unsuccessful). The patient was subsequently randomized to treatment with sofosbuvir-velpatasvir and completed 12 weeks of

treatment per protocol. He reported mild to moderate headaches during treatment. The patient achieved a sustained virologic response 12 weeks after the completion of treatment as determined by the central laboratory using the COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test, version 2.0 (Roche Molecular Systems), with a lower limit of quantification of 15 IU per milliliter.

Deep sequencing of samples collected at baseline from all enrolled patients in the ASTRAL study was performed by the Sponsor as described previously (1). In this case, using genotype 2 specific primers, no amplification product was obtained. In all cases when amplification failed for the baseline samples, we repeated amplification of NS5B short fragments and performed population sequencing. In this patient a short NS5B fragment (amino acids 227-338) was successfully amplified. Phylogenetic analysis comparing this population sequence with reference sequences representing all known subtypes of HCV(2) indicated the patient was infected with a novel subtype of genotype 7 HCV. As we do not have specific primers for amplification of genotype 7 NS5A and NS5B, random-primer based full genome amplification was used to amplify the full length HCV (3). All RNA in the sample was amplified and deep sequenced. Reads obtained from deep sequencing were assembled and the resultant full genome HCV sequence confirmed the genotype 7 determination (Figure 1). Phylogenetic analysis of sequences from four patients with genotype 7 HCV suggests that this patient's virus is most closely related to the virus from isolate QC272 (4). (Figure 2)

Discussion

Phase 3 studies demonstrated that treatment with the combination of sofosbuvir-velpatasvir for 12 weeks was well tolerated and results in high SVR12 in patients with genotype 1-6 HCV infection (1,5). Ours is the first published case demonstrating that sofosbuvir-velpatasvir can be

effective in a patient with genotype 7 infection, and suggests that genotype 7 HCV infected patients may be considered for treatment with sofosbuvir-velpatasvir. This case additionally confirms the pangenotypic activity of sofosbuvir-velpatasvir and suggests that determination of HCV genotype may not be required prior to treatment with this potent DAA combination. Sofosbuvir-velpatasvir has the potential to become an important regimen for treatment of HCV infection in regions of the world where HCV genotyping is expensive, inaccurate, or unavailable. However, in the meantime, it may be advisable for patients originating from Democratic Republic of Congo to be sequenced fully to minimize the risk of misclassifying and subsequently treating patients with a sub-optimal treatment regimen.

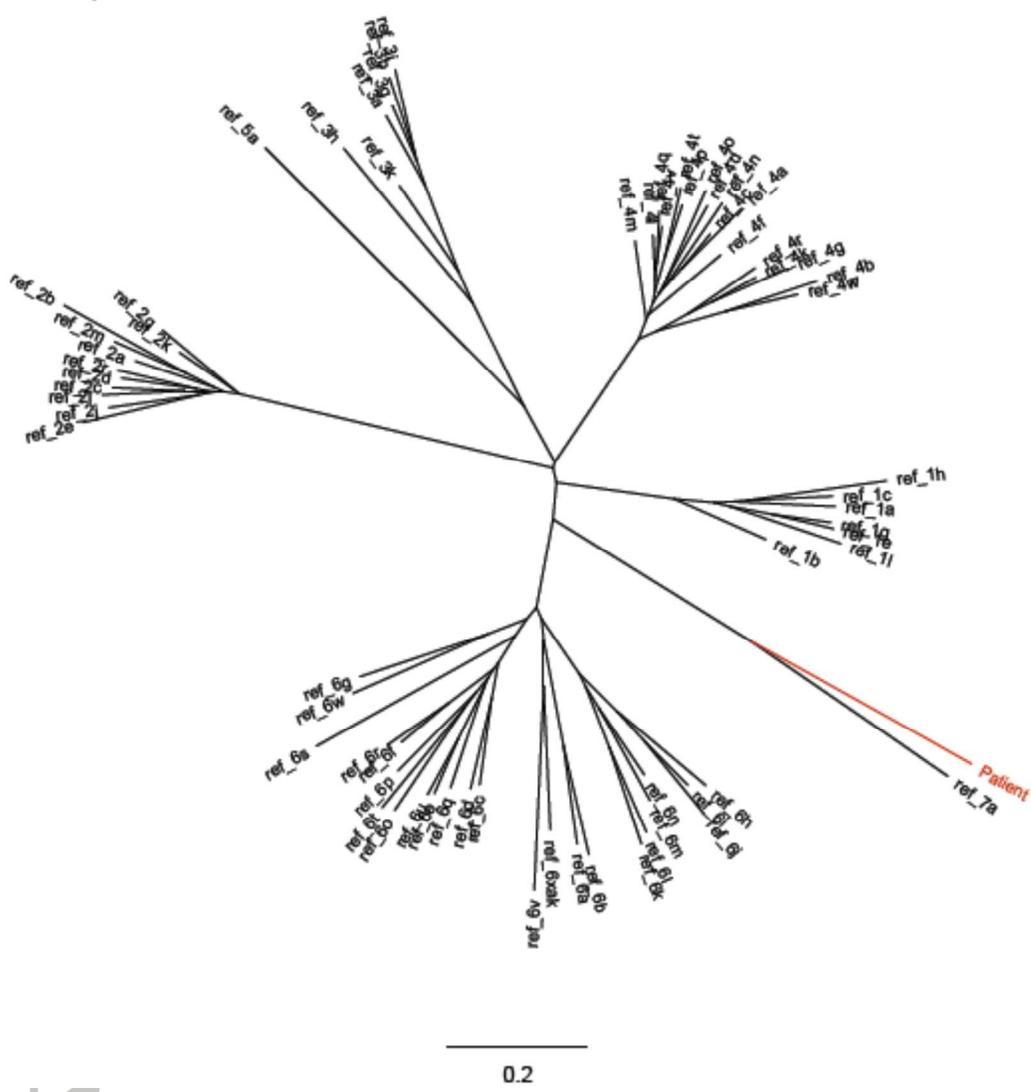
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Figure 1. Phylogenetic comparison of HCV isolated from patient with known HCV subtypes
(The sequence used for this analysis is a segment of the full length sequence: NS5B: 1-325)



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Figure 2. Phylogenetic comparison of HCV isolated from patient with previously reported genotype 7 isolates (The sequence used for this analysis is a segment of the full length sequence: NS5B: 227-338)

