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Successful Treatment of Mixed Hepatitis C Genotypes in a Cirrhotic Patient With an All-Oral, Interferon-Free Regimen

Ayman Ahmed Sakr, MD, MSc, PhD1,2, Jasmine M. Hanifi, MD3, and Ming Valerie Lin, MD1,4
1Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women’s Hospital, Boston, MA
2Tropical Medicine, Menoufi University Faculty of Medicine, Shebin El-Kom, Egypt
3Department of Internal Medicine, Brigham and Women’s Hospital, Boston, MA
4Harvard Medical School, Boston, MA

ABSTRACT
Mixed hepatitis C virus (HCV) genotype infection is emerging with improved methods of detection. It is commonly seen in hemodialysis patients and intravenous drug users due to repeated HCV exposure and absence of protective immunity, and can contribute to treatment failure. Direct-acting antiviral regimens have been extensively studied in patients with different individual HCV genotypes; however, there are no reported data on their use in patients with mixed HCV genotype. We present a case of mixed HCV genotype 1a and 2 infection in a decompensated cirrhotic patient treated successfully with sofosbuvir, ledipasvir, and ribavirin.

INTRODUCTION
Hepatitis C virus (HCV) is an enveloped positive single-stranded RNA virus that replicates in the cytoplasm using an RNA-dependent RNA polymerase, which lacks general proofreading ability, resulting in at least 1 mutation per replicative cycle. This frequent mutation allows for rapid acquisition of viral mutations and resistance variants.1-3 Efficacious and well-tolerated interferon-free, all oral, direct-acting antiviral (DAA) regimens have been extensively studied in patients with individual HCV genotypes. However, there are no reported data on the use of DAAs in patients with mixed HCV genotype.

CASE REPORT
A 58-year-old man with history of intravenous drug and alcohol abuse, seizure disorder, and chronic HCV infection (treatment naïve) with decompensated cirrhosis, model for end-stage liver disease (MELD) 10, and Child-Turcotte-Pugh class B, complicated by bleeding esophageal varices status after banding and nadolol, and hepatic encephalopathy on lactulose, presented to the liver clinic for HCV treatment evaluation. Other medications included levetiracetam, carbamazepine, and omeprazole. Physical exam revealed anicteric sclera, spider angiomata, and palmar erythema. Abdominal examination was benign with no overt ascites. There was no asterixis. Initial laboratory studies showed HCV genotype 1a and 2, HCV viral load 2,100,000 IU/mL, negative HIV antibody, white blood cell count 6,000/μL, hemoglobin 11.5 g/dL, platelets 227 K/μL, aspartate aminotransferase 49 U/L, alanine aminotransferase 35 U/L, alkaline phosphatase 122 U/L, total bilirubin 1.5 mg/dL, albumin 3.1 g/dL, creatinine 0.86 mg/dL, and international normalized ratio 1.2.

The patient was started on sofosbuvir 400 mg, ledipasvir 90 mg, and ribavirin 200 mg daily (dose adjusted as tolerated) for 24 weeks. He was compliant and denied any side effects, and he remained clinically stable. Hemoglobin remained above 10 mg/dL during the treatment period. The patient had negative HCV viremia and normal liver function tests at treatment weeks 4, 12, and 24. The patient missed lab work at 12 weeks after treatment and had...
and sequencing millions of DNA strands in parallel. Molecular clonal sequences at a much lower concentration genotypes and variations. This allowed us to identify next-generation sequencing, elevate the detection rate of typing, such as polymerase chain reaction, Sanger, and reported prevalence and incidence of mixed genotype HCV reinfection. Repeated HCV genotyping should also be considered throughout treatment can contribute to treatment failure. This has been demonstrated by several case reports of treatment failure with a treatment to avoid liver disease progression.

DISCUSSION

Mixed HCV genotype infection is defined as the detection of multiple genetically distinct HCV strains at a single time point as a result of either coinfection or superinfection. The reported prevalence and incidence of mixed genotype HCV infection range from 0% to 39% and 25.3%, respectively. Mixed genotype HCV infection is more commonly encountered in patients with repeated risk exposures such as hemodialysis patients, intravenous drug users, and multitransfused patients (eg, hemophiliacs).

The traditional line-probe genotyping detects less than 5% of the minor HCV variants (minor variation in viral sequence) and likely contributes to the underestimation of mixed genotype HCV infection. Novel methods of HCV genotyping, such as polymerase chain reaction, Sanger, and next-generation sequencing, elevate the detection rate of genotypes and variations. This allowed us to identify molecular clonal sequences at a much lower concentration and sequencing millions of DNA strands in parallel.

Hepatitis C virus genotyping is a standard practice prior to HCV treatment initiation; however, the use of advanced genotyping methods should be considered throughout treatment of high-risk individuals because underlying mixed HCV infection can contribute to treatment failure. This has been demonstrated by several case reports of treatment failure with a different HCV genotype strain without an apparent risk of reinfection. Repeated HCV genotyping should also be considered in patients with ongoing risk of HCV exposure, especially if there is a viral breakthrough during treatment. If the same subtype as the initial infection is detected, Sanger sequencing would be helpful in discriminating relapse from reinfection.

The HCV RNA sequence is 9.6 kb long and encodes a single polyprotein that is cleaved into 3 structural proteins (core, E1, and E2) and 7 nonstructural (NS) proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B). The viral NS5A protease cleaves the HCV polyprotein at downstream junctions. NS4B and NS5A appear to play key roles in replication. The virus-specific enzymatic functions of the NS3/4A protease and the NS5B RNA-dependent RNA polymerase have made them the focus of initial DAA development.

Between 2001 and 2011, the standard of care for patients with chronic HCV infection was the combination of pegylated interferon and ribavirin. This yielded a SVR rate of 40-50% in genotype 1 infection and 70-80% in genotype 2 and 3 infections. The first DAA was approved by the U.S. Food and Drug Administration in 2011. It consisted of boceprevir and telaprevir (NS3/4A protease inhibitor) in combination with pegylated interferon and ribavirin for genotype 1 infection. The first-generation DAAs increased the SVR rate to 60-70%. In December 2013, sofosbuvir (NS5B polymerase inhibitor) was approved. It was recommended to be used with pegylated interferon and ribavirin for 12 weeks in genotype 1 and genotype 4 infections, and with ribavirin alone for 12 weeks in genotype 2 and for 24 weeks in genotype 3. As of October 2015, ledipasvir (NS5A inhibitor) was approved and has since been recommended for use in combination with sofosbuvir for patients with genotype 1 and 4-6 infections. Grazoprevir (NS3/4A protease inhibitor) and elbasvir (NS5A inhibitor) with or without ribavirin for 12 or 18 weeks in patients with genotypes 1, 4, and 6 were recently approved in January 2016. It is the first DAA regimen that can be used in patients with renal failure. The current DAA regimens have even higher SVRs of more than 80-90%, depending on the genotype. The currently available DAAs are still genotype-specific with most of the drugs potent against genotype 1. There have been several clinical trials published recently reporting high efficacy and safety of sofosbuvir and a pangenotypic NS5A inhibitor, velpastasvir, in mixed patient populations (eg, treatment experienced and cirrhotic) with HCV genotype 1-6 infections. The treatment efficacy was greater than 90% in most circumstances. It was also noted to be well tolerated with minimal side effects. The approval of pangenotypic treatment would simplify and streamline HCV treatment and address the emergence of mixed HCV genotype infection. However, until it becomes available, patients with mixed HCV genotype would still benefit from genotype-specific treatment to avoid liver disease progression.

DISCLOSURES

Author contributions: All authors wrote the article. MV Lin is the article guarantor.

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Informed consent was obtained for this case report.

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