An Hepatitis C Virus (HCV)/HIV Co-Infected Patient who Developed Severe Hepatitis during Chronic HCV Infection: Sustained Viral Response with Simeprevir Plus Peginterferon-Alpha and Ribavirin

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Abstract

We herein describe the case of a 42-year-old man who developed severe hepatitis caused by hepatitis C virus (HCV) infection at 14 years after the start of human immunodeficiency virus (HIV) treatment. Surprisingly, the levels of alanine aminotransferase (ALT) fluctuated, reaching a peak higher than 1,000 IU/L during chronic HCV infection, and the hepatic histology showed advanced liver fibrosis at 3 years after the primary HCV infection. He was treated with simeprevir, peginterferon-alpha, and ribavirin with a sustained viral response. We conclude that HCV/HIV co-infected patients need to commence anti-HCV therapy when the levels of ALT fluctuate severely under successful HIV control.

Key words: hepatitis C virus, human immunodeficiency virus, co-infection, simeprevir, peginterferon-alpha, severe hepatitis

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Introduction

Co-infection with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) is common, as both viruses share similar modes of transmission (1). Although injection drug use (IDU) remains the main route of HCV infection, recent studies have shown that HCV can be sexually transmitted in the absence of IDU, particularly among HIV-positive men who have sex with men (MSM) (2-5). In general, the progression of HCV-related liver diseases is accelerated in HCV/HIV co-infected individuals (6, 7). HCV has emerged as an important cause of morbidity and mortality in co-infected patients (8) because successful combination antiretroviral therapy (cART) has dramatically changed the prognosis of HIV-infected individuals (9). The consequences of HCV/HIV co-infection are less spontaneous clearance (10), higher rates of chronicity, accelerated fibrosis

progression with increased risk of cirrhosis (11, 12) and hepatocellular carcinoma (13) resulting in higher liver-related mortality, and decreased HCV treatment response (14, 15). The management of HCV infection among the HIV-infected population poses a serious challenge for physicians. Recently, a better sustained viral response (SVR) has been seen following combination therapy of HCV protease inhibitor simeprevir and peginterferon-alpha/ribavirin (PegIFN α /RBV) (16). This combination therapy may be a suitable treatment regimen for HCV-positive Japanese patients because the interferon-resistant HCV genotype 1b is more common in Japan (17). This report herein describes a case of a MSM who developed severe hepatitis caused by chronic HCV infection while under successful cART, and who achieved SVR through HCV treatment with simeprevir and PegIFN α /RBV.

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Table. Laboratory Data before Treatment of Hepatitis C.

Blood cells		Blood chemistry		Serological test	
RBCs	557×10 ⁴ /μL	Albumin	4.4 g/dL	HBs antigen	0.01 mIU/mL (negative)
Hemoglobin	16.2 g/dL	AST	32 IU/L	HBs antibody	219.93 mIU/mL (positive)
Hematocrit	48.3%	ALT	49 IU/L	HBc antibody	4.40 Sample/c (positive)
WBCs	5,200 /μL	Alkaline phosphatase	187 IU/L	HBV DNA	not detected
Neutrophils	55.9%	γ-glutamyl transferase	112 IU/L	HCV antibody	10.69 Sample/c (positive)
Lymphocytes	29.6%	Total bilirubin	1.4 mg/dL	HCV serotype	undetermined
Platelets	15.5×10 ⁴ /μL	Blood urea nitrogen	10 mg/dL	HCV RNA	6.8 Log IU/mL
CD4 cells	376 /μL	Creatinine	0.79 mg/dL	HIV-1 RNA	not detected
CD4/CD8 ratio	1.0	Hyaluronic acid	148 ng/mL (<50)	<i>IL 28B</i> SNP	Major homo
PT (INR)	1.24	PIIINP	1.2 U/mL (<1.0)	α fetoprotein	6 ng/mL
		Type IV collagen 7S	8.4 ng/mL (<6.0)	PIVKA II	24 mAU/mL

RBC: red blood cell, WBC: white blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase, PIIINP: amino-terminal properties of type III collagen, PT (INR): prothrombin time (International Normalized Rate)

Case Report

A 42-year-old Japanese man was diagnosed with an HIV-1 infection at our hospital in August 1997. He is a MSM and had no other risk of liver damage (e.g., ingestion of alcohol or the presence of diabetes mellitus). At his initial laboratory examination, his HIV-1 viral load was 75,000 copies (3.8 log copies)/mL, and his CD4-positive cell count was 160/μL. The patient began treatment with two nucleoside analogue reverse transcriptase inhibitors (NRTIs) in 1997, which was common before treatment with cART was established and is now contraindicated. Nelfinavir was added to his treatment regimen after its approval by the Japanese Ministry of Health and Welfare in 1998; however, this treatment failed because of viral drug resistance. The nelfinavir-related resistant amino acid mutation D30N was detected on his HIV drug resistance test. The subsequent regimen consisted of didanosine (ddl), abacavir (ABC), and ritonavir-boosted atazanavir; these drugs were selected for salvage treatment and afterwards, the virus was well controlled. In 2011, the cART regimen was updated to ABC, etravirine (ETR), and raltegravir (RAL) to aid in preventing ddl long-term toxicity, lactic acidosis due to mitochondria injury, lipodystrophy, neuropathy, and portal vein embolization. The patient's HIV viral load was undetectable and his CD4 count was maintained above 350/μL for 15 years after the salvage treatment was initiated. At 14 years after the introduction of antiretroviral treatment, his alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels rose to 601 IU/L and 268 IU/L, respectively, and the anti-HCV antibody was seroconverted, thus leading to the clinical diagnosis of acute HCV infection. There was no evidence of hepatitis A, B, D, or E infection, or evidence of other causes of hepatic cytolysis; the patient reported having had unprotected receptive anal intercourse with multiple men the previous year but had never injected illicit drugs. His HCV RNA load was 6.3 log IU/mL, however, the HCV serotype was indeterminable. One month after the onset of acute hepatitis, his ALT level decreased to under 200 IU/L and further decreased to less than 100 IU/L after 4 months.

Because his platelet count was over 180,000/μL and the noninvasive biomarkers of liver fibrosis (18, 19) did not indicate advanced liver fibrosis [hyaluronic acid: 60.7 μg/L (normal: <50 μg/L), amino-terminal properties of type III collagen: 1.1 U/mL (normal: <1.0 U/mL), type IV collagen 7S: 5.3 ng/mL (normal: <6.0 ng/mL)], the HCV treatment was suspended until direct-acting antivirals (DAAs), which are highly effective, well-tolerated therapies (20), were approved by the Japanese Ministry of Health, Labour and Welfare. Two years after the onset of his primary HCV infection, the patient's liver transaminases were again elevated (ALT 1,100 IU/L, AST 541 IU/L) and the exacerbation of his HCV infection was supported by HCV RNA fluctuations (his HCV load was 6.2 to 7.2 log IU/mL). A percutaneous liver biopsy was performed 3 years after the diagnosis of his primary HCV infection and indicated advanced fibrosis with active hepatitis (grade 3 inflammation and stage 3 fibrosis based on the New Inuyama Classification), but no steatohepatitis or other type of liver injury was observed. The patient was treated with simeprevir and PegIFNα-2b/RBV for 24 weeks while estimating the presence of HCV genotype 1 infection, because the result of HCV serotyping by an enzyme-linked immunosorbent assay using group-specific recombinant peptides for the NS4 region (21) was undetermined. The cART regimen was changed to rilpivirine (RPV)/RAL for HCV treatment, because both RPV and RAL have relatively few drug-drug interactions with simeprevir. The patient achieved SVR without severe complications (including possible HIV virological rebound) and his ALT level returned to within the normal range. The laboratory data before the start of HCV therapy is summarized in Table. *IL28B* single nucleotide polymorphisms (TT genotype) were found (22). The overview of the clinical course of our case is shown in Figure.

Discussion

Elevated ALT levels against primary HCV infection are reported to be mild and relatively transient in HIV-infected MSM (23). The present case is a MSM who showed HCV seroconversion with a high ALT level (elevated to 601 IU/L)

Figure. The clinical course of our case.

under successful cART. Surprisingly, his ALT levels fluctuated and elevated to over 1,000 IU/L 2 years after his primary HCV infection. In general, chronic hepatitis caused by HCV mono-infection exhibits a mild increase in ALT, rarely over 300 IU/L, because HCV-specific T-cell responses became dysfunctional over several months after the primary infection (24, 25). Moreover, during HIV infection, impaired CD4⁺ T-cells function and the subsequent depletion of CD4⁺ T-cells, as a result of continuous CD4⁺ cell destruction, is thought to be a cause of the profound impaired cellular immune response which has an important role in viral hepatitis. However, in this HCV/HIV co-infected patient, his liver inflammation two years after the primary HCV infection represented severe hepatitis (ALT levels peaking at > 1,000 IU/L) beyond the chronic HCV mono-infected conditions. These findings indicated that the immune responses against HCV infection could not completely recover in HIV-infected individuals even after long-term treatment with successful cART regimens. HIV infection is well known as an immune suppressive disease but its essentially an immune disorder. Many clinicians actually face diverse immune disorders, including not only immune suppressive disease characterized by a susceptibility to infection with opportunistic pathogens, but also autoimmune diseases (such as thyroid diseases, psoriasis, systemic lupus erythematoses, and inflammatory bowel syndrome) after the immune system recovers following cART. The causes of induced autoimmune diseases remain unknown, however, it is believed that functional impairments on regulatory T-cells (Tregs), sustained even after starting cART, contributes to induce dysregulated

inflammation. Therefore, we hypothesize that the reason for a strong cellular immune response during HIV infection is due to the fact that CD4⁺ Tregs can be infected with HIV-1 (26), and the Treg function may not have fully recovered even though the patient's HIV infection had been well controlled by successful cART regimens for more than 15 years. Although direct evidence for this hypothesis is lacking, it was previously reported that impaired Treg function may have detrimental consequences for the control of HCV immune activation (27) and accelerated fibrosis progression. Indeed, our patient's hepatic histology 3 years after the primary HCV infection presented as F3 (pre-cirrhosis stage), indicating the very rapid progression of liver fibrosis from the HCV infection in an HIV-infected individual even though the CD4⁺ T-cell counts recovered. Therefore, careful monitoring for the rapid progression of hepatitis C is required for HIV-infected individuals even after successful HIV control.

In HCV/HIV co-infected patients, cART has shown to delay the progression of liver cirrhosis (28), and those with undetectable HIV RNA levels tend to have slower cirrhosis progression than those with detectable viremia (29). However, in the present case, the HIV RNA levels were repeatedly undetectable, and the hepatic histology showed the development of pre-cirrhosis due to severe liver inflammation. Therefore, treating the HCV with active hepatitis was required to halt the fibrosis progression. The response to treatment with PegIFNα/RBV in HCV/HIV co-infected patients is poorer than that of patients with HCV mono-infection. In fact, the SVR rate is reported to be 27-29% (30-32) in co-

infected patients compared with 42-46% (33, 34) in HCV genotype 1 mono-infections. It is expected that DAA will be a good therapy for HCV/HIV co-infected individuals. Co-infected patients receiving concurrent HIV and HCV treatment, however, are faced with the difficulty of proper treatment regimen selection, such as an increased risk of drug-drug interactions and drug-induced liver injury, particularly among those with advanced liver disease (35). HIV integrase inhibitors (i.e., RAL) have relatively few drug-drug interactions, whereas the use of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitor (NNRTI), except RPV, might preclude the use of some HCV DAA agents, particularly those targeting HCV protease. The patients are sometimes forced to change cART regimens because HCV proteases are metabolized through CYP3A4 and HIV protease inhibitors and NNRTIs interfere with the CYP3A4 activity, which may affect the HCV protease blood concentration. Therefore, we selected RAL and RPV as the NRTI-sparing regimen, because RPV has fewer drug-drug interactions and this combination is effective for HIV suppression with minimal side effects. In a phase II study, treatment with telaprevir (a first-generation HCV NS3/4A protease inhibitor) and PegIFN α /RBV for 48 weeks led to significantly greater responses in HCV/HIV co-infected patients, with SVR rates of 74% (36). The second-generation HCV protease inhibitor simeprevir, a once-daily HCV protease inhibitor with more favorable tolerability, has also been studied in co-infected populations. When given for 12 weeks in combination with PegIFN α /RBV to co-infected individuals with HCV genotype 1, the overall SVR at 12 weeks was 74% (37). Because simeprevir can interact with HIV protease inhibitors and efavirenz (an NNRTI), most patients in that study were placed on RAL-based cART.

For many patients, it is clear that there is a benefit to waiting for the approval of new DAA agents as interferon-free treatment regimens. However, immediate HCV therapy should be strongly considered for co-infected patients with advanced fibrosis or active hepatitis. For HCV treatment-naïve co-infected patients, we recommend that immediate cART initiation should be considered and the degree of fibrosis should be examined in each patient. A liver biopsy may be required for the co-infected patients, because reduced platelet counts are more commonly observed among patients infected with HIV (38, 39) and noninvasive scoring systems are still in the early use in HIV co-infected patients.

In conclusion, HCV/HIV co-infected patients under successful HIV control, especially those with primary HCV infection after HIV infection, must be carefully monitored to evaluate both the progression of hepatitis and the initiation of anti-HCV therapy, even if the noninvasive biomarkers of liver fibrosis indicate decreased fibrosis.

The authors state that they have no Conflict of Interest (COI).

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