

Analysis of the hepatic functional reserve, portal hypertension and prognosis of patients with HIV/HCV co-infection through contaminated blood products in Japan

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Key words: non-cirrhotic portal hypertension, highly active antiretroviral therapy,
contaminated blood products, hemophilia, liver transplantation.

**The authors were supported by a Grant-in-Aid for Research on HIV/AIDS from
the Ministry of Health, Labor, and Welfare of Japan, the “Eguchi project”.**

**This paper was presented at the 13th Congress of the Asian Society of
Transplantation (CAST2013)**

Abstract

Background: As the survival of HIV-infected individuals has improved due to the widespread use of antiretroviral therapy, the mortality rate due to HCV-related liver disease has increased in HIV/HCV co-infected patients. **Aim: 1.** To establish the appropriate therapeutic strategy for HIV/HCV co-infected patients by evaluating the liver function, including the hepatic functional reserve and portal hypertension. **2.** To investigate the prognosis of HIV/HCV co-infected patients in Japan. **Patients and Methods: 1.** In addition to regular liver function tests, the hepatic functional reserve of 41 patients with HIV/HCV co-infection was evaluated by the indocyanine green retention rate and liver GSA-scintigraphy. **2.** The data for 146 patients with HIV/HCV co-infection through blood products were extracted from four major HIV centers in Japan. In addition to liver function tests, the platelet counts (PLT) were evaluated as a marker of portal hypertension. **Results: 1.** In spite of the relatively preserved general liver function test results, approximately 40% of the HIV/HCV co-infected patients had an impaired hepatic functional reserve. In addition, while the albumin and bilirubin levels were normal, the platelet count (PLT) was less than 150,000/ μ L in 17 patients. **2.** Compared with HCV mono-infected patients with a PLT less than 150,000 μ L, the survival of HIV/HCV co-infected patients was shorter (HCV: 5 years, 97%; 10 years,

86% and HIV/HCV: 5 years, 87%; 10 years, 73%, $p < 0.05$). **Conclusion:** These results must be taken into account to establish an optimal therapeutic strategy, including the appropriate timing of liver transplantation in HIV/HCV co-infected patients in Japan.

Introduction

From 1970 until the early 1980's, blood products were imported to Japan, and contaminated blood products were unknowingly used to treat patients with hemophilia. It was later revealed that these patients were sometimes infected with both HIV and HCV (HIV/HCV co-infection)¹. However, as the survival of HIV-infected people has improved due to the widespread use of antiretroviral therapy, the mortality due to HCV-related liver disease has increased in HIV/HCV co-infected patients^{2,3}.

The main aim of this investigation was to investigate 1. The status of portal hypertension and the prognosis in HIV/HCV co-infected patients, 2. To establish an appropriate therapeutic strategy for HIV/HCV co-infected patients, including the timing of liver transplantation, in Japan.

Patients and Methods

For Aim 1, routine hematology and blood chemistry tests (general liver function), abdominal ultrasonography and contrast-enhanced CT were performed for 30 patients with HIV/HCV co-infection at Nagasaki University Hospital. To investigate the hepatic functional reserve, liver GSA-scintigraphy and the ICG retention test at 15 min

were performed. In addition, upper gastrointestinal tract endoscopy to diagnose gastroesophageal varices was performed.

For Aim 2, the data of 146 patients who had acquired HIV/HCV co-infection through blood products were extracted from four major HIV centers in Japan, including the AIDS Clinical Center, Osaka National Hospital, Yokohama Municipal Hospital and Kyushu Medical Center. In addition to liver function tests, platelet counts were evaluated as a marker of portal hypertension. As a control, HCV mono-infected patients from Nagasaki Medical Center were used for comparison.

Results

In spite of the relatively well-maintained general liver functions, approximately 40% of the HIV/HCV co-infected patients had an impaired hepatic functional reserve (Table 1). In addition, in spite of maintained albumin and bilirubin levels, the platelet count was less than 150,000 /ul in 17 co-infected patients, indicating the presence of ongoing portal hypertension.

Even with Child-Pugh A liver function, the HIV/HCV co-infected patients showed a worse prognosis than the HCV mono-infected patients. The prognosis was especially poor in those with lower platelet counts than in the patients with a normal

platelet count (Table 2). When compared with HCV mono-infected patients with a platelet count less than 150,000 ul, the survival of HIV/HCV co-infected patients was much shorter (HCV: 5 years, 97%; 10 years, 86% and HIV/HCV: 5 years, 87%; 10 years, 73%, $p < 0.05$).

Discussion

In HIV/HCV co-infected patients, liver failure due to HCV hepatitis was previously reported to be enhanced by ART-related hepatotoxicity, especially manifesting as non-cirrhotic portal hypertension (NCPH).^{4,5} One of the ART drugs, Didanosin (DDI), has been suspected to under the serious morbidity observed in co-infected patients.⁶ Thus, not only in patients with deteriorated liver function, such as in Child-Pugh B or C cases, but also even in Class A cases, the patients' liver function can easily deteriorate abruptly.⁷ The natural course of pure NCPH is unknown, because it can be modulated by HCV or other causes, and has only been reported as case series. An important study of "NCPH in HIV mono-infected patients without HCV" was published in 2012.⁸ All five patients had portal hypertensive symptoms, such as ascites or variceal bleeding, after receiving antiretroviral therapy.

Therefore, all HIV/HCV co-infected patients should be carefully followed up so as not to miss an opportunity for LT.⁹ The prognosis for HIV/HCV co-infected patients was reported to be worse than that for HCV mono-infected patients.¹⁰ In the present study, co-infected patients with a platelet count less than 150,000 μL had an especially poor prognosis, with a shorter survival than mono-infected patients. Our results should be taken into account to establish a therapeutic strategy, while also considering the appropriate timing of liver transplantation in HIV/HCV co-infected patients.

In 2013, based on the evidence of rapid progression of the liver cirrhosis and portal hypertension in patients with HIV/HCV co-infection, a rank-up system for the waiting list for deceased donor LT was set up in Japan. Even HIV/HCV co-infected liver cirrhotic patients with Child-Pugh class A can be listed for LT as “point 3” because of the PCPH nature. Co-infected patients with Child-Pugh class B and C disease can be listed as “point 6” and “point 8” based on the data collected by the HIV/AIDS project team of the Ministry of Health, Labor, and Welfare of Japan, and the published literature.¹¹ This primarily covers victims who received contaminated blood products for hemophilia.

Future perspectives on liver transplantation for HIV/HCV co-infection

1. New anti-HCV agents should be developed to improve the control against HCV.

2. New ART drugs, such as Raltegravir, should facilitate post-transplant immunosuppressive therapy.
3. Non-invasive tests for portal hypertension, such as the fibroscan, should be performed for hemophilic patients
4. The development of guidelines for the management hemophilia in the perioperative period should facilitate better outcomes.

In conclusion, the present results should be taken into account to establish an optimal therapeutic strategy, including the appropriate timing of liver transplantation in HIV/HCV co-infected patients.

References

1. Eguchi S, Soyama A, Hidaka M, Takatsuki M, Muraoka I, Tomonaga T, et al. Liver transplantation for patients with human immunodeficiency virus and hepatitis C virus coinfection with special reference to hemophiliac recipients in Japan. *Surg Today*. 2011;41:1325-31.
2. Merchante N, Merino E, Lopez-Aldeguer J, Jover F, Delgado-Fernandez M, et al. Increasing incidence of hepatocellular carcinoma in HIV-infected patients in Spain.

HIV/AIDS 2013;56:143-50.

3. Cusinato CT, Koetz AP, Barcellos NT, Wolff FH. The prevalence of cirrhosis and hepatocellular carcinoma in patients with human immunodeficiency virus infection. *Hepatology* 2013;57:249-57.
4. Vispo E, Moreno A, Maida I, Barreiro P, Cuevas A, Albertos S, et al. Noncirrhotic portal hypertension in HIV-infected patients: unique clinical and pathological findings. *AIDS*. 2010;24:1171-6.
5. Mendizabal M, Craviotto S, Chen T, Silva MO, Reddy KR. Noncirrhotic portal hypertension: another cause of liver disease in HIV patients. *Ann Hepatol*. 2009;8:390-5.
6. Kovari H, Ledergerber B, Peter U, Flepp M, Jost J, Schmid P, et al. Swiss HIV Cohort Study. Association of noncirrhotic portal hypertension in HIV-infected persons and antiretroviral therapy with didanosine: a nested case-control study. *Clin Infect Dis*. 2009;49:626-35.
7. López-Diéguez M, Montes ML, Pascual-Pareja JF, Quereda C, Von Wichmann MA, Berenguer J, et al. GESIDA 37/03-FIPSE 36465/03-NEAT IG5 Study Group. The natural history of liver cirrhosis in HIV-hepatitis C virus-coinfected patients. *AIDS*. 2011;25:899-904

8. Jackson BD, Doyle JS, Hoy JF, Roberts SK, Colman J, Hellard ME, et al.
Non-cirrhotic portal hypertension in HIV mono-infected patients. *J Gastroenterol Hepatol* 2012;17:1512-1519.
9. Soyama A, Eguchi S, Takatsuki T, Hidaka M, Muraoka I, Kanematsu T. Analysis of hepatic functional reserve in HIV_HCV co-infected patients. *Acta Hepatol Japonica (KANZO)* 2012;53:403-8. (In Japanese)
10. Takatsuki M, Eguchi S, Soyama A, Kanematsu T, Nakao K, Shirasaka T, et al.
Evaluation of portal hypertension and prognosis of patients with HIV-HCV co-infection through contaminated blood product. *Acta Hepatol Japonica (KANZO)* 2012;53:586-90. (in Japanese)
11. Eguchi S, Takatsuki M, Kuroki T. Liver transplantation for patients with human immunodeficiency virus and hepatitis C virus co-infection: update in 2013. *J Hepatobiliary Pancreat Sci.* 2013 Sep 11(E-pub ahead of print)

Table 1. Patient characteristics

Child-Pugh A/B/C	38(93%)/1(2%)/2(5%)
ICG R15 (%)	
<10/10-20/20-30/30<	24(59%)/8(20%)/3(7%)/6(14%)
GSA schincigram LHL15	
>0.9/0.8-0.9/0.8>	28(69%)/6(15%)/7(16%)
Liver configuration on CT	
Normal/CH/LC	10(24%)/17(42%)/14(34%)
Splenomegaly	
Yes/No	26(63%)/15(37%)
Esophageal varices	
Yes/No	13(32%)/28(68%)

Table 2. Patient survival after diagnosis

	5Y OS	10Y OS	
HCV mono-infection (Child-Pugh A)	97%	86%	
HIV/HCV co-infection (Child-Pugh A)			
Platelets > 150,000	94%	85%	
Platelets < 150,000	87%	73%	p<0.05 vs. HCV mono infection