Seroconversion of acute hepatitis B by antiretroviral therapy in an HIV-1 infected patient

Mahoko Ikeda-Kamimura[1,2], Masahide Horiba[1]

(1) Division of Respiratory Medicine, National Hospital Organization, Higashi-Saitama Hospital ; (2) Department of Infectious Diseases, Graduate school of Medicine, the University of Tokyo, Japan.

Abstract

A 33-year-old man with human immunodeficiency virus type1 (HIV-1) infection was admitted because of acute hepatitis B. His serum alanine aminotransferase level was 1200 IU/mL and CD4 cells count was 268/mm³. Antiretroviral therapy including tenofovir and emtricitabine, which suppresses both HIV and hepatitis B virus (HBV) replication, was initiated. The liver enzymes decreased dramatically. The viral loads of both HIV-1 and HBV were suppressed below detectable limits. Seroconversion from hepatitis B surface antigen to hepatitis B surface antibody was acquired 19 weeks later. In this case, the initiation of antiretroviral therapy with anti-HBV activity during the acute phase of hepatitis B had a favourable effect on HBV serostatus. (Acta gastroenterol. belg., **2010**, 73, **389-391**).

Key words : acute hepatitis B, HIV co-infection, seroconversion, tenofovir, emtricitabine

Introduction

Treatment of persistent hepatitis B with human immunodeficiency virus type 1 (HIV-1) coinfection involves several challenges. First, spontaneous seroconversion is rare, and therefore, acute hepatitis B frequently progresses to the chronic phase (1). Second, antiretroviral therapy (ART) might induce severe hepatotoxicity and more rapid progression to liver cirrhosis than the natural course due to potent immune reconstitution to hepatitis B virus (HBV) (2).

According to the U.S. Department of Health and Human Services (DHHS) guidelines for HIV management, it is recommended that an ART regimen that contains at least two drugs with anti-HBV effects should be used for chronic hepatitis B and HIV co-infected patients. However, the time point at which to start the ART is still under discussion in these cases. We show here a favourable clinical course of an HIV / HBV coinfected patient who was treated with HBV-effective ART in the acute phase of hepatitis B.

Case report

A 33-year-old man was admitted to our hospital because of acute hepatitis for two weeks. He was a man who had sex with men and was diagnosed with HIV-1 infection 4 years before. He had since been followed at our outpatient clinic. His CD4 counts have been maintained at around 300 /mm³ during the follow-up period without ART.

At first visit, anti-cytomegalovirus antibody was positive ; however, other serological markers such as hepatitis B surface antigen (HBsAg), HBs antibody, hepatitis B core antibody and anti-hepatitis C antibody were negative. He did not consume alcohol, smoke, or take illicit drugs. He was diagnosed with syphilis and treated with amoxicillin at that time.

On admission, he had no symptoms such as fever, general fatigue or jaundice. Physical examination revealed no apparent abnormalities. His laboratory data showed elevated liver enzymes, and his serum asparate aminotransferase (ALT) level was 1,200 IU/L. Total bilirubin and coagulation activity were within normal limits (Table I). HBsAg and hepatitis B envelope antigen (HBeAg) were positive, and anti-hepatitis B core antibody immunoglobulin type M was also detected at the 32.0 cut-off index with no detection of immunoglobulin type G three weeks after the first detection of elevated liver enzymes. HBV DNA was more than 7.6 log copies/mL. HBV genotype was Ae. According to these laboratory data, he was diagnosed with acute phase hepatitis B. His serological markers did not suggest any other causes of hepatitis, such as hepatitis A or hepatitis C.

Since ALT was decreased to 985 IU/L after supportive therapy and bed rest for a week, he was discharged on the 17th hospital day. However, on his next visit to the outpatient clinic on day 7 after discharge, his ALT was elevated again to 1,343 IU/L. His CD4 cell count was 268/mm³ and HIV-RNA was 14,000 copies/mL. No mutations of reverse transcriptase and protease of HIV-1 associated with resistance to ART were detected. HBV DNA polymerase tyrosine-methionine-asparate-asparate (YMDD) motif mutations, which induce resistance to lamivudine, were not detected.

ART with combination of one protease inhibitor, lopinavir/ritonavir (LPV/r ; lopinavir 600 mg/day, ritonavir 200 mg/day) and two non-nucleoside/nucleotide reverse transcriptase inhibitors that had efficacy against hepatitis B virus, tenofovir disoproxil fumarate (TDF,

Correspondence to : Dr. Masahide Horiba, 4147 Kurohama, Hasuda, Saitama 349-0196, Japan. Tel. : 048-768-1161. Fax : 048-769-5347. E-mail : horibam@nhs.hosp.go.jp

Submission date : 14/04/2009
Acceptance date : 22/11/2009

Table I-a. — **Results of hematologic and serum chemical laboratory tests on admission**

Variable	Reference range	Results	Variable	Reference range	Results
WBC (/mm^3)	3500-8500	5210	Albumin (g/dL)	4.0-5.0	4.0
Hemoglobin (g/dL)	13.5-17.0	15.2	Total bilirubin (mg/dL)	0.3-1.2	0.69
Hematocrit (%)	40.0-50.0	46.4	AST (IU/mL)	13-33	436
Platelet count (10^4/mm^3)	15.0-35.0	18.3	ALT (IU/mL)	8-42	1206
PT (%)	70-100	92.9	LDH (U/L)	119-229	375
APTT(sec)	26-41	37	Gamma-GTP (IU/L)	10-47	234
Fibrinogen (mg/dL)	160-410	218	ChE (IU/L)	168-470	278
			Amylase (IU/L)	42-132	54
CD4$^+$ cell count (/mm^3)		268	CRP (mg/dL)	0-0.2	0.15
HIV-RNA (copies/mL)	Less than 50	14,000			

Abbreviations in Table I-a) (In alphabetical order)
APTT ; activated partial thromboplastin time, ALT ; alanine aminotransferase, AST ; aspartate aminotransferase, BUN ; blood urea nitrogen, ChE ; cholinesterase, CRP ; C-reactive protein, GTP ; gamma glutamyl transpeptidase, HIV-RNA ; human immunodeficiency virus-RNA, LDH ; lactate dehydrogenase, PT ; prothrombin time, WBC ; white blood cells.

Table I-b. — **Results of Microbiologic and Serologic Laboratory Tests**

Variable	Reference range	Results	Variable	Reference range	Results
HBs-Ag		Positive	HBc-IgM		Positive
HBs-Ab		Negative	HBc-IgG		Negative
HBe-Ag		Positive	HA-Ab (IgG)		Negative
HBe-Ab		Negative	HA-Ab IgM		Negative
HBV-DNA (log copies/mL)	< 2.6	> 7.6	HCV-Ab		Negative

Abbreviations in Table I-b) (In alphabetical order)
HBs-Ag ; hepatitis B surface antigen, HBs-Ab ; hepatitis B surface antibody, HBe-Ag ; hepatitis B envelope antigen, HBe-Ab ; hepatitis B envelope antibody, HBV-DNA ; hepatitis B virus-DNA, HBc-IgM ; hepatitis B core antibody immunoglobulin type M, HBc-IgG ; hepatitis B core antibody immunoglobulin type G, HA-Ab (IgG) ; hepatitis A antibody immunoglobulin type G, HA-Ab (IgM) ; hepatitis A antibody immunoglobulin type M.

300 mg/day) and emtricitabine (FTC, 200 mg/day) were initiated five weeks after elevated liver enzymes were firstly documented. ALT quickly decreased to normal range within 4 weeks. Furthermore, seroconversion from HBe antigen to HBe antibody occurred at the same time. Moreover, HIV-RNA was decreased to less than 50 copies/mL. HBV-DNA also decreased to less than 2.6 log copies/mL at 11 weeks after initiating ART. The CD4 cell count was increased to 481/mm^3 40 weeks later. No adverse effects were observed and he did not develop an immune reconstitution syndrome (IRS) to HBV. He finally achieved complete seroconversion including clearance of HBsAg and generation of HBs antibody (HBsAb) 19 weeks after initiating ART.

Discussion

We showed here that the administration of ART with 2 anti-HBV agents in a patient who had both acute hepatitis B and chronic HIV-1 infection resulted in HBV seroconversion without any adverse events. Both HIV-1 and HBV viral loads were suppressed under the detectable limit ; furthermore, seroconversion of HBsAg was acquired. It has been reported that even if ART with two HBV effective drugs is initiated, HBsAg seroconversion rarely occurs in the chronic phase of HBV/HIV-1 coinfection. One study indicated that in chronic hepatitis B with HIV infection, only 2 of 59 HBeAg positive patients and 2 of 23 HBeAg negative patients achieved HBsAg seroconversion with ART containing lamivudine and/or tenofovir (3). Usually, HBV-effective ART can suppress HBV viral load but cannot always achieve HBsAg seroconversion. Total extermination of HBV in HIV-1 coinfected patients is difficult in the chronic phase of hepatitis B. In this case, it is speculated that the favourable effect of ART was induced by the suppression of HBV in accordance with immune reconstitution, which assisted in the production of antibodies to HBV. A previous report showed that reconstitution of both HBV-specific CD4-positive and CD8-positive T-cell responses occurs with restoration of CD4-positive T-cell counts after initiation of antiretroviral therapy (4). Previously in Japan, genotype B and C viruses have been predominantly found in hepatitis B patients (5). Chronic hepatitis defined as persistent HBsAg for more than 6 months. Chronicity varies depending on genotype and age. Recently, genotype A, especially subtype Ae, has been found more frequently than genotype B and C viruses, which were previously most common in hepatitis B patients in Japan (6). Some studies showed that genotype A was the most frequent type of chronicity, with rates from 8.7% to 23% (6, 7).

The management of acute hepatitis B is difficult because almost all cases of acute hepatitis B recover spontaneously in immunocompetent adults. No differences between a lamivudine-treated group and placebo group were detected in terms of HBV seroconversion among immunocompetent adults with acute hepatitis B

(8). However, the clinical course of acute hepatitis B in HIV/HBV coinfected patients is different from that in immunocompetent patients. Hadler *et al* reported that chronic HBV infection developed in 21% of HIV-infected patients compared to 7% of controls with HBV alone after exposure to HBV infection (1). Once hepatitis B progresses to the chronic phase, it remains the most important cause of hepatocellular carcinoma (9). In patients with HIV/HBV coinfection, the clinical course shows more rapid progression to liver cirrhosis or hepatocellular carcinoma. A higher mortality rate was observed in patients with HIV/HBV coinfection than in those with either virus alone (10).

Before entecavir became available, first-line chronic hepatitis B treatment among non-HIV patients was lamivudine. Since lamivudine alone is not potent enough to suppress HBV continuously, HBV mutations emerge several years later. For example, long-term single use of lamivudine induces the development of YMDD motif mutations. Its emergence rate is 49% in patients with lamivudine after a median duration of treatment of 32.4 months (11). YMDD mutations cause flare-ups of hepatitis B and more rapid progression to cirrhosis or hepatocellular carcinoma under the treatment of lamivudine alone (12). HIV infected patients generally have high titer of HBV-DNA and probably have more risk of emergence of YMDD mutation.

In summary, we report complete seroconversion of HBV with the use of HBV-effective ART in a patient with acute hepatitis B coinfected with HIV. However, the possibility remains that ART might induce serious flare-up of hepatitis B by a potent immune reconstitution syndrome to HBV. Therefore, we propose that careful consideration be taken when deciding to initiate acute hepatitis B treatment in each HIV coinfected patient.

Acknowledgement

All authors had no conflicts of interest.

References

1. HADLER S.C., JUDSON F.N., O'MALLEY P.M., ALTMAN N.L., PENLEY K., BUCHBINDER S., SCHABLE C.A., COLEMAN P.J., OSTROW D.N., FRANCIS D.P. Outcome of hepatitis B virus infection in homosexual men and its relation to prior human immunodeficiency virus infection. *J. Infect. Dis*., 1991, **163** : 454-9.
2. DRAKE A., MIJCH A., SASADEUSZ J. Immune reconstitution hepatitis in HIV and hepatitis B coinfection, despite lamivudine therapy as part of HAART. *Clin. Infect. Dis*., 2004, **39** : 129-32.
3. MIAILHES P., TRABAUD M.A., PRADAT P., LEBOUCHE B., CHEVALLIER M., CHEVALLIER P., ZOULIM F., TREPO C. Impact of highly active antiretroviral therapy (HAART) on the natural history of hepatitis B virus (HBV) and HIV coinfection : relationship between prolonged efficacy of HAART and HBV surface and early antigen seroconversion. *Clin. Infect. Dis*., 2007, **45** : 624-32.
4. LASCAR R.M., LOPES A.R., GILSON R.J., DUNN C., JOHNSTONE R., COPAS A., REIGNAT S., WEBSTER G., BERTOLETTI A., MAINI M.K. Effect of HIV infection and antiretroviral therapy on hepatitis B virus (HBV)-specific T cell responses in patients who have resolved HBV infection. *J. Infect. Dis*., 2005, **191** : 1169-79.
5. ORITO E., ICHIDA T., SAKUGAWA H., SATA M., HORIIKE N., HINO K., OKITA K., OKANOUE T., IINO S., TANAKA E., SUZUKI K., WATANABE H., HIGE S., MIZOKAMI M. Geographic distribution of hepatitis B virus (HBV) genotype in patients with chronic HBV infection in Japan. *Hepatology*, 2001, **34** : 590-4.
6. OZASA A., TANAKA Y., ORITO E., SUGIYAMA M., KANG J.H., HIGE S., KURAMITSU T., SUZUKI K., TANAKA E., OKADA S., TOKITA H., ASAHINA Y., INOUE K., KAKUMU S., OKANOUE T., MURAWAKI Y., HINO K., ONJI M., YATSUHASHI H., SAKUGAWA H., MIYAKAWA Y., UEDA R., MIZOKAMI M. Influence of genotypes and precore mutations on fulminant or chronic outcome of acute hepatitis B virus infection. *Hepatology*, 2006, **44** : 326-34.
7. SUZUKI Y., KOBAYASHI M., IKEDA K., SUZUKI F., ARFASE Y., AKUTA N., HOSAKA T., SAITOH S., KOBAYASHI M., SOMEYA T., MATSUDA M., SATO J., WATABIKI S., MIYAKAWA Y., KUMADA H. Persistence of acute infection with hepatitis B virus genotype A and treatment in Japan. *J. Med. Virol*., 2005, **76** : 33-9.
8. KUMAR M., SATAPATHY S., MONGA R., DAS K., HISSAR S., PANDE C., SHARMA B.C., SARIN S.K. A randomized controlled trial of lamivudine to treat acute hepatitis B. *Hepatology*, 2007, **45** : 97-101.
9. HASSAN M.M., HWANG L.Y., HATTEN C.J., SWAIM M., LI D., ABBRUZZESE J.L, BEASLEY P., PATT Y.Z. Risk factors for hepatocellular carcinoma : synergism of alcohol with viral hepatitis and diabetes mellitus. *Hepatology*, 2002, **36** : 1206-13.
10. THIO C.L, SEABERG E.C., SKOLASKY R., JR., PHAIR J., VISSCHER B., MUNOZ A., THOMAS D.L., Multicenter AIDS Cohort Study. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet*, 2002, **360** : 1921-6.
11. LIAW Y.F., SUNG J.J., CHOW W.C., FARRELL G., LEE C.Z., YUEN H., TANWANDEE T., TAO Q.M., SHUE K., KEENE O.N., DIXON J.S., GRAY D.F., Sabbat J., Cirrhosis Asian Lamivudine Multicentre Study Group. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N. Engl. J. Med*., 2004, **351** : 1521-31.
12. BESSESEN M., IVES D., CONDREAY L., LAWRENCE S., SHERMAN K.E. Chronic active hepatitis B exacerbations in human immunodeficiency virus-infected patients following development of resistance to or withdrawal of lamivudine. *Clin. Infect. Dis*., 1999, **28** : 1032-5.