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Short communication

Antiviral treatment for human immunodeficiency virus patients co-infected with hepatitis B virus: combined effect for both infections, an obtainable goal?

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Abstract

A large percentage of human immunodeficiency virus (HIV) patients have serological evidence of a past or present hepatitis B virus infection (HBV). Long-term survival is increasing for HIV patients because of highly active antiretroviral therapy. Therefore, the chronic hepatitis B infection may become an important determinant of disease outcome in these co-infected patients. We describe two HIV/HBV co-infected patients who were treated with extended antiviral therapy, initially indicated for the HIV infection. Lamivudine, a suppressor of viral replication in both infections, was one of these antiviral drugs. One patient showed a severe rebound of the HBV after withdrawal of lamivudine, the other patient developed a mutant hepatitis B virus after 18 months of treatment. This mutation was exclusively induced by lamivudine. These patients show that, with improved HIV-related survival, the HBV infection should be monitored carefully, thereby enabling the physician to interfere with therapy when necessary.

Keywords: Hepatitis B virus; Human immunodeficiency virus; Lamivudine; Lamivudine withdrawal hepatitis; Resistance; Triple therapy

About 80% of HIV-1 positive patients have serological evidence of past or present HBV infection (Sinicco et al., 1997). With the introduction of triple therapy for HIV-1 infected patients and

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the expectation of markedly prolonged survival, the consequences of chronic HBV infection in HIV-1 infected patients are becoming clinically relevant and a determinant of survival.

Lamivudine, the (−)-enantiomer of 2′-deoxy-3′-thiacytidine, is virus suppressive in both HIV-1 infection and HBV infection (Benhamou et al., 1995; Eron et al., 1995). In addition, antiretroviral therapy may restore immunity through suppression of HIV-1 RNA and repopulation of the immune system. This adds to eradication of the HBV (Carr and Cooper, 1997). Furthermore, nucleoside analogues used for HIV-1 infections have been reported to cause lactic acidosis and liver steatosis (Olano et al., 1995). Special attention should be paid to these associated effects in patients with manifest liver disease, especially cirrhosis, as hepatic failure might be prevented.

Lamivudine can induce mutations in the YMDD motif of the HBV DNA polymerase gene in both HIV-1 and HBV (Boucher et al., 1993; Ling et al., 1996; Honkoop et al., 1997; Niesters et al., 1998). Withdrawal of lamivudine is usually followed by reactivation of HBV infection, detectable by rising HBV DNA levels. In some patients this surge of viral replication is followed by a hepatitis flare with elevated alanine aminotransferase (ALT) levels (Honkoop et al., 1995).

Based on our experience in two patients co-infected with HIV-1 and HBV, we would like to focus attention on two syndromes associated with the use or withdrawal of lamivudine.

Patient A, a 49-year-old man, initially visited our clinic in March 1990. Routine laboratory testing before surgery revealed liver function disorders. Subsequently he was found to be HBsAg positive and HBeAg positive. In addition to the HBV infection an HIV-1 infection was diagnosed. On physical examination no major abnormalities were detected, except for a genital herpes infection. Laboratory testing showed: no abnormalities other than aspartate aminotransferase (AST) 41 U/l (5-30 U/l), ALT 81 U/l (5-30 U/l) and CD4 cell count 0.46×10^9/l ($0.5\text{-}1.57 \times 10^9$/l). Serum markers of HBV infection were: HBsAg positive; anti-HBc positive; HBeAg positive; anti-HBs negative; anti-HBe negative (IMx, Abbott, Chicago, IL) and HBV DNA 2.75×10^9 geq (genome equivalents)/ml (Eurohep standard (Gerlich et al., 1995), measured as 275 pg/ml in Genostics assay; Abbott). Other markers were anti-HCV (hepatitis C virus) negative, anti-HDV (hepatis D virus) negative, anti-CMV (cytomegalovirus) negative.

A liver biopsy showed a chronic persistent hepatitis with mild periportal fibrosis.

Because of a decline of CD4 positive cells, zidovudine (AZT) monotherapy was started in February 1992. Lamivudine was added in December 1993 (Fig. 1). During this treatment, the HBV infection became inactive according to non-detectable HBV DNA and HBeAg. The loss of HBeAg was associated with a hepatitis flare. HIV-1 RNA levels (Roche Monitor 1.0, Somerville, NJ), however, remained high ($> 1 \times 10^4$ geq/ml). In 1996, therapy was changed to stavudine, didanosine and indinavir triple therapy; lamivudine was withdrawn. HIV-1 RNA levels dropped markedly, even below detection levels, but stabilized around 10^3 geq/ml. CD4 cell counts increased from 0.16×10^9/l to above 0.2×10^9/l. Three months after discontinuation of lamivudine, HBV DNA rose to 3.7×10^9 geq/ml (measured as 12 010 pg/ml in Digene assay; Murex, UK), accompanied by a rise of HBeAg. Five months after cessation of lamivudine, ALT had risen to more than 600 U/l. At this moment HBV DNA levels had become undetectable by liquid hybridization again after the reintroduction of lamivudine. This was followed by a rapid decrease to normal ALT levels in December 1996. Up until March 1998 the HBV infection was still suppressed (HBV DNA negative by polymerase chain reaction (PCR), HBeAg negative), and serum ALT was normal.

In March 1994, patient B, a 48-year-old man was admitted to our hospital because of marked elevation of his liver enzymes. He was found to be HBV and HIV-1 positive.

On physical examination no significant abnormalities were detected. Laboratory results were: platelets 102×10^9/l ($140\text{-}360 \times 10^9$/l); CD4 cell count 0.08×10^9/l ($0.5\text{-}1.57 \times 10^9$/l); prothrombin time 13.0 s (9.3-12.3 s); bilirubin 20 μmol/l (4-14 μmol/l); alkaline phosphatase 84 U/l (25-75 U/l); γGT (gamma-glutamyltransferase) 71 U/l (5-35 U/l); AST 249 U/l (5-30 U/l); ALT 295 U/l (5-30

U/l); albumin 32 g/l (36-48 g/l); IgG 36.3 g/l (8-18 g/l); HBsAg positive; HBeAg positive; anti-HBc positive; anti-HBe negative (IMx, Abbott, Chicago, IL); HBV DNA 2.77×10^9 geq/ml (measured as 277 pg/ml in Genostics assay; Abbott, USA); anti-HAV (IgM) positive; anti-HCV negative; anti-HDV negative; anti-HIV-1 positive.

The liver biopsy showed cirrhosis, chronic moderate active hepatitis with lobular involvement and collapse. The ultrasound of the upper abdomen showed hepatosplenomegaly and ascites.

Because of his low CD4 cell count, priority was given to HIV-1 therapy. Treatment was started with zidovudine 250 mg twic a day and co-trimaxol 480 mg once a day; half a year later lamivudine 300 mg twice dailyd was added. The medication was tolerated well.

During lamivudine therapy, HBV DNA fell below detection level in November 1994 (Fig. 2). HBeAg quantified with a Paul Ehrlich standard as reference and expressed in PEU (Paul Ehrlich units) declined from 487 PEU/ml to 0.9 PEU/ml in October 1995. HBe seroconversion did not occur. Concordant with the decline in virus levels, transaminase activity also declined to normal levels (below 30 U/l).

One and a half years after starting lamivudine (mid 1996), while the patient was still taking lamivudine and zidovudine, a sudden rise in HBV DNA and HBeAg levels, followed by a rise of ALT to levels above 200 U/l, was documented. Sequencing of the YMDD motif of the C-domain of the DNA polymerase of HBV showed a mutation at position 552 at which methionine was replaced by valine, indicating lamivudine resistance. Lamivudine was continued as ALT levels had fallen spontaneously and there was fear of lamivudine withdrawal hepatitis in a patient with cirrhosis. Because of continued elevated levels of HIV-1 RNA up to 9×10^4 geq/ml, in October 1996 zidovudine was replaced by didanosine, stavudine, indinavir; the dose of lamivudine was reduced to 150 mg twice daily. Bilirubin rose markedly after the change in therapy which was attributed to interference of indinavir with bilirubin metabolism; stable levels of prothrombin time, albumin and bile acids excluded progressive liver damage. ALT levels continued to fall and were back to normal at the beginning of 1997.

The response of HIV-1 to the present medication is satisfactory with HIV-1 RNA below detection levels of quantitative PCR ($< 5.0 \times 10^2$

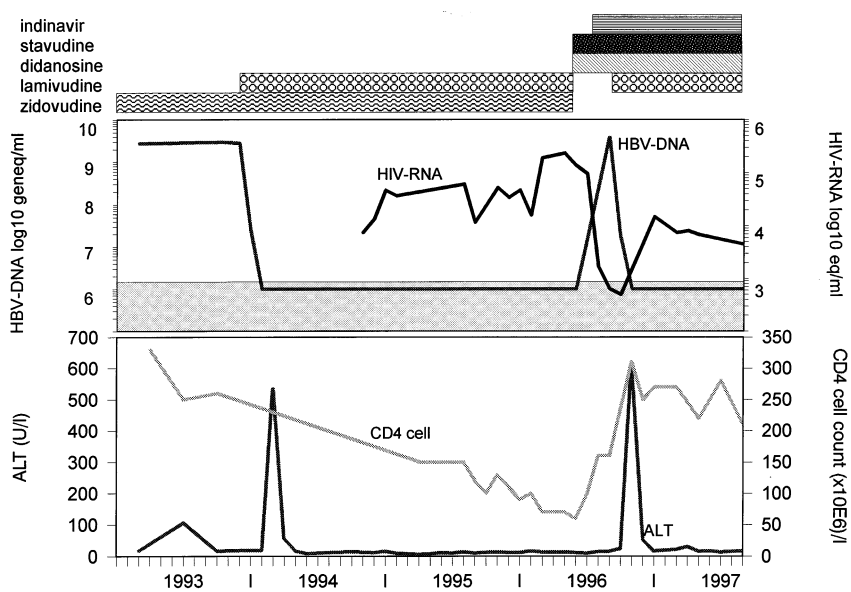

Fig. 1. HIV-1 HBV co-infection. Patient A. The profound virus suppressive effect of lamivudine and the hepatitis episode associated with HBeAg loss after withdrawal of lamivudine is illustrated.

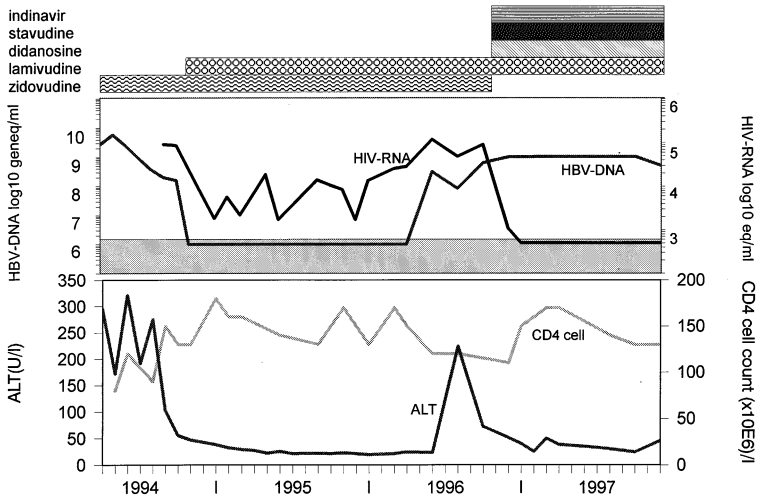

Fig. 2. HIV-1 HBV co-infection. Patient B. The profound hepatitis B virus suppressive effect of lamivudine and the reappearance of HBV DNA (lamivudine resistance), followed by a hepatitis flare is illustrated.

geq/ml), but only a marginal rise in CD4 cell count to 0.13×10^9/l was observed. An active HBV infection with levels of HBV DNA up to 1.0×10^9 geq/ml and HBeAg up to 4120 PEU/ml is still present, apparently without a detectable immune response.

Chronic HBV infection does not influence the progression of HIV-1 infection to AIDS (Gilson et al., 1997; Sinicco et al., 1997). In contrast, HIV-1 infection does influence the course of HBV infection. Acute hepatitis B progresses to chronic hepatitis B in 5-10% of HIV-1-negative adults; in those who are positive for HIV-1 the chronicity rate has been reported to be 40% (Sinicco et al., 1997). Chronic hepatitis B patients who are HIV-1 infected have a less pronounced tendency to show a spontaneous decrease in viral replication than those who are HIV-1 negative (Gilson et al., 1997; Krogsgaard et al., 1987). In addition, antiretroviral therapy can restore immunity and induce recovery from HBV (Carr and Cooper, 1997).

Our study shows that patients with HIV-1/HBV co-infection undergoing multiple treatments with nucleoside analogues can manifest hepatitis flares associated with drug-induced resistance or with withdrawal.

A lamivudine withdrawal hepatitis flare, as seen in patient A, with ALT levels over ten times the upper limit of normal, occurs in 16% of immunocompetent patients. Usually these flares pass without clinically significant symptoms; in a minority of the patients jaundice is seen (Honkoop et al., 1999). Re-institution of lamivudine therapy reduces viral replication rapidly; simultaneously, the activated cytotoxic T cells can eliminate the remaining hepatocytes that express viral antigen. In our patient, suppressed viral replication with elevated immune response led to undetectable HBV DNA by PCR and loss of HBeAg.

Patient B became resistant to lamivudine reflected in a sudden rise of HBV DNA after 14 months of treatment. In immunocompetent patients, resistance to lamivudine develops in 39% (actuarial cumulative incidence) at 1 year (Honkoop et al., 1997). In HIV-1 HBV co-infected patients, lamivudine resistance to HBV has not been described in the cohort of 40 patients with a progressive HIV-1 infection co-infected with HBV treated with lamivudine for 12 months (Benhamou et al., 1996). Insensitivity of the HBV for lamivudine has been described in liver transplant recipients who showed a recurrence of viral replication starting after 6 months

of lamivudine treatment (Tipples et al., 1996; Aye et al., 1997; Bartholomew et al., 1997; de Man et al., 1998). A mutation in the highly conserved YMDD motif of the reverse transcriptase gene is described to be the cause of the decreased sensitivity to this drug. In patient B, substitution of valine for methionine at position 552 of the YMDD motif in the C-domain, which is explicitly linked to the leucine to methionine mutation at position 528 in the B-domain of the polymerase gene, was seen. After stopping lamivudine, the dominant virus population returned to the wild type, with accelerated viral replication and possible risk of hepatitis flare.

With the increased efficacy of triple therapy causing prolonged survival of HIV-1 infected patients, HBV infection may become an important determinant of disease outcome in these patients. Overlap in therapy for these two viral infections should be monitored carefully since change in therapy because of non-response to lamivudine of one disease (HIV infection) might cause reactivation of the other (hepatitis B).

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