Caso clinico

Case report

In vivo antiviral activity of telbivudine against HIV-1: a case report

Attività antivirale in vivo *di telbivudina contro HIV-1: descrizione di un caso clinico*

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INTRODUCTION

It is estimated that 5-10% of the 40 million people infected with human immunodeficiency virus (HIV) worldwide are co-infected with hepatitis B virus (HBV), because both viruses are transmitted through the same routes [1, 2]. All HIV/HBV co-infected subjects should be assessed to determine whether HIV or HBV treatment, both or neither are indicated. Tenofovir (TDF), lamivudine (3TC) and emtricitabine (FTC) are available for HBV treatment, but are also active against HIV: the double antiviral activity precludes their use in monotherapy in patients who are HIV/HBV co-infected and who are not eligible to receive highly active antiretroviral therapy (HAART) due to the risk of selecting resistant mutations in HIV genome [2, 3]. Even monotherapy with entecavir, which was not long ago considered a valid option, is now considered contraindicated, because anti-HIV activity of entecavir and the consequent emergence of relevant resistance mutations (M184V) were recently described [2, 3]. Telbivudine (LdT) is a synthetic nucleoside analogue that inhibits replication of HBV [4]. However, due to its relatively low genetic barrier (and therefore high rate of selecting resistant strains), telbivudine use in clinical practice is limited. It is noteworthy that telbivudine has two advantages over several analogues: its safety in pregnancy (it is classified in pregnancy category B together with tenofovir) and the lack of a proven effect on HIV [5]. This latter peculiar antiviral activity would present an opportunity to use LdT for the treatment of HBV infection in patients co-infected with HIV without leading to the risk of developing HIV resistance in the absence of HAART [2-4, 6, 7]. We describe the case of a HIV/HBV coinfected patient who showed a reduction in HIV viral load associated with LdT use.

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CASE PRESENTATION

A 42-year-old male patient was admitted to our Department in May 2003 with an acute hepatitis B and HIV-1 coinfection CDC stage A1. He was a smoker, and his body mass index was 30 kg/m^2. Antibodies for hepatitis C virus (HCV) and hepatitis A virus (HAV) were negative. The patient was not taking any drugs.

At the admission the patient presented aspartate aminotransferase (AST) higher by 10-fold, alanine aminotransferase (ALT) higher by 23-fold, hepatitis B surface antigen (HBsAg) positive, IgG and IgM for hepatitis B core (HBc) positive, hepatitis B e antigen (HBeAg) positive, hepatitis B e antibody (HBeAb) negative, HBV DNA >2x10^6 copies/ml (COBAS Amplicor® PCR Assay; HBV lower limit of quantification 200 copies/ml), HIV RNA 3,800 copies/ml (Amplicor® PCR Assay; HIV lower limit of quantification <50 copies/ml), CD4+ lymphocytes 832/mmc. In June 2004, the patient pre-

sented elevated AST (by 2-fold) and ALT (by 3-fold) and did not clear HBV. Due to high CD4 counts and well controlled HIV infection, he was not prescribed antiretrovirals.

A liver biopsy was performed and it showed chronic hepatitis with minimal-mild activity (grading 4 and staging 1-2 according to Ishak classification). Because of the persistence of HBsAg and elevated ALT, therapy with pegylated interferon (IFN)-α2a 180 μg weekly was initiated. This treatment was withdrawn after one month for exacerbation of psoriasis and grade 3 thrombocytopenia. In 2008 HBV DNA sequencing test revealed the presence of HBV genotype A, without 3TC, adefovir (ADV) and entecavir resistance-conferring mutations. At this time, laboratory data showed HBV DNA >38,000 U.I./ml (COBAS AmpliPrep®/COBAS TaqMan®, with a detection limit of 12 U.I./ml and a dynamic range from 20 to $1.7x10^7$ U.I./ml), HIV RNA 3,900 copies/ml (log 3.59) (AmpliPrep®/COBAS TaqMan, with a detection limit of 20 copies/ml and a dynamic range from 30 to $1x10^7$ U.I./ml), CD4+ 1,145/mmc, ALT higher by 2-fold, glomerular filtration rate (GFR) was 90 mL/min. Due to persistent good viro-immunological status, monotherapy with ADV was started. After 6 months HIV viral load remained unchanged (3,150 copies/ml), HBV DNA was 166,000 U.I./ml, and ALT higher by 2-fold. Therefore LdT was added. After eight weeks of therapy with LdT/ADV, HIV RNA was 125 copies/ml (log 2.09) and HBV DNA was 914 U.I./ml. After five months of the same therapy, the patient obtained ALT normalization, seroconverted to anti-HBe, achieved HBV DNA undetectability; HIV RNA was 145 copies/ml. On March 2010, after 10 months of combined LdT/ADV treatment, the patient began complaining of severe myalgia and weakness. GFR remained between 88 and 96 ml/min during this period. The possible causes of mussels pains were investigated: serum sodium, calcium, phosphate, creatine kinase, lactate, autoantibodies, thyroid hormones were normal. No other drug was prescribed or taken by the patient. LdT and ADV were withdrawn and the patient started a HAART regimen (TDF/FTC/raltegravir). At baseline of HAART, HIV-RNA was 217 copies/ml (log 2.34).

DISCUSSION

In HIV/HBV coinfected patients authoritative international guidelines recommend starting HAART, irrespective from HIV virological and immunological status. The same guidelines, alternatively, recommend, in patients with very good immunological status (CD4 count >500 mmc), treatment with a drug directed only against HBV such as pegylated IFN, ADV and LdT [8]. Literature data are conflicting regarding the anti-HIV activity of LdT. In fact LdT does not interfere with HIV replication *in vitro* while some authors reported its *in vivo* activity against HIV. Milazzo et al. reported three cases of HIV/HBV co-infected patients, treated for HBV infection with LdT monotherapy and followed up without treatment interruption for 24 weeks [9]. In all three patients, LdT produced a rapid and potent reduction in HBV DNA levels. In two of the three patients, HIV viral load declined by 2-3 logs copies/ml and became undetectable (<300 copies/ml) within 1 to 2 weeks from the start of LdT treatment but subsequently rebounded to the baseline levels within 4 weeks of treatment. The remaining patient had no change in the HIV-1 viral load from the baseline level throughout the duration of treatment. Viral sequencing analysis showed that all three patients had wild-type HIV-1 strain and no mutations conferring resistance were found in either HIV-1 or HBV at up to 24 weeks of follow-up. The Authors stated that the reduction in the HIV-1 viral load may be caused by LdT, but also by lymphocyte activation, cytokine production, and liver inflammation, i.e., effects that resulted indirectly from the blocking of HBV replication by LdT [2, 9].

Low et al. reported a single case of a HIV/HBV coinfected patient, who was receiving ADV-LdT combination therapy and had a surprising reduction in the HIV-1 viral load that rebounded after LdT was withdrawn. Interestingly after a 2-week rechallenge with LdT, HIV viral load dropped again by more than one log. However no *in vitro* confirmation testing of susceptibility to either ADV or LdT was performed, and no drug resistance-conferring mutation was reported [2, 10].

Similarly, our case clearly shows an *in vivo* effect of LdT on HIV in a HIV/HBV coinfected patient. We acknowledge that LdT was not given alone but in combination with ADV. However we underline that ADV given alone during the previous six months did not cause an inhibitory effect on HIV replication. Moreover one could speculate that the potentially nephrotoxic drug ADV as well as LdT are excreted by the kidney and reduced kidney function could

increase ADV-levels which is known to have intrinsic anti-HIV activity. However renal function remained normal during the whole period. Other studies, most performed *in vitro*, denied an effect of LdT on HIV. In detail, Lin et al. evaluated LdT *in vitro* antiviral activity in eight distinct HIV clinical isolates. They observed no direct inhibition in replicative activity [2].

Finally Van Maarseveen et al. analyzed viral dynamics as well as genotypic and phenotypic resistance development in two HIV/HBV coinfected individuals treated with LdT. This treatment did not modify HIV-1 viral load nor select genotypic or phenotypic resistance in HIV-1 reverse transcriptase or demonstrate significant alterations *in vitro.* Therefore they conclude that LdT has no *in vitro* and *in vivo* anti-HIV-1 activity [7].

Finally, considering the two options provided by guidelines in HIV/HBV coinfected patients:

1) using HAART regardless of virological and immunological status;
2) using an "only HBV-targeted drug" (as LdT) when CD4+ are >500 mmc, and although literature is not concordant on a role of LdT on HIV, our case suggests to exert caution in employing LdT in HIV positive patients. Therefore, in the management of similar cases, we recommend to employ HAART even in cases of optimal immunological status [8].

CONCLUSIONS

Our case shows an early reduction of HIV-1 viral load associated with LdT use. This enforces the concern of possible antiviral activity of LdT against HIV-1, as demonstrated in other few cases reported in literature, and therefore of selecting resistant mutations in HIV genome.

Due to in *vitro/in vivo* conflicting data, the antiviral activity and the biochemical properties of LdT against HIV needs to be further investigated in both clinic and laboratory details.

Keywords: HIV, HBV, telbivudine, coinfection, HAART.

SUMMARY

The treatment of HBV infection in patients with HIV co-infection presents several peculiar features: some drugs active against HBV are also active against HIV. This precludes their use in monotherapy in HIV/HBV co-infected patients due to the potential risk of selecting HIV-resistant strains. Telbivudine seemed to be a candidate for exclusive anti-HBV therapy because it exerts no significant *in vitro* activity against HIV. In this context, we describe the case of a HIV/HBV co-infected patient who presented indication for treatment only for HBV infection. After a short course of PEG-interferon treatment withdrawn due to adverse events, adefovir monotherapy was started. Since no significant viral drop was achieved during adefovir treatment, telbivudine was added. This treatment was associated with a complete virological response on HBV. It is noteworthy that after two months of this treatment even the HIV viral load presented a significant reduction. Our findings pose concerns of possible antiviral activity of telbivudine against HIV and therefore of selecting resistant mutations.

RIASSUNTO

Il trattamento dell'infezione da HBV in pazienti anti-HIV positivi presenta diversi aspetti peculiari. Tra gli altri, alcuni farmaci efficaci contro HBV mostrano anche attività contro HIV. Ciò preclude il loro utilizzo in monoterapia nei pazienti HIV/HBV coinfetti per il rischio di selezionare ceppi di HIV resistenti. La telbivudina sembrava essere un candidato per una terapia esclusiva anti-HBV poiché non esercita significativa attività in vitro *contro HIV. Descriviamo il caso di un paziente HIV/HBV coinfetto che presentava indicazione al trattamento solo per l'infezione da HBV. Dopo un breve ciclo di terapia con PEG-interferone, sospeso per eventi avversi, veniva iniziata monoterapia con adefovir. Poiché non si osservava alcun decremento significativo della viremia di HBV durante il trattamento con adefovir, veniva aggiunta telbivudina. Tale trattamento era associato ad una risposta virologica completa per HBV. Tuttavia dopo 2 mesi di terapia con telbivudina, anche HIV-RNA presentava una riduzione significativa. Il caso presentato aumenta le preoccupazioni circa l'attività antivirale di telbivudina contro HIV e quindi del rischio di selezionare mutanti di HIV resistenti.*

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