Salvage therapy with tenofovir followed by adefovir maintenance in a cirrhotic patient with a lamivudine resistant HBV flare

Terapia di salvataggio con tenofovir seguita da terapia di mantenimento con adefovir in paziente cirrotico lamivudino-resistente con elevata viremia e flare di ALT

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INTRODUCTION

Viral resistance complicates the course of lamivudine (LAM) therapy in chronic hepatitis B, HBeAg negative, at a rate of about 15% per year [1]. To prevent the clinical consequences of resistance a close monitoring of HBV-DNA levels using a sensitive PCR assay is recommended. Rescue therapy with adefovir dipivoxil (ADV) should be added as soon as an increase in viremia of 1 log is detected [2]. If not so, viremia increases and a clinical breakthrough appears, which may lead to hepatitis flares and jaundice. In these circumstances, ADV is less effective and patients may rapidly worsen, particularly when cirrhosis is present [2, 3]. Antiviral treatment of these patients requires a drug with potent and rapid anti-HBV action. Entecavir is active against LAM resistant HBV, but its activity and genetic barrier is lower as compared with wild type HBV [4]. Tenofovir (TDF) belongs to nucleotide analogue class, is active against LAM resistant HBV strains and is rapid and potent even in the presence of high HBV-DNA levels (5-7). At present, it is on the way to be licensed for chronic hepatitis B in many countries. Here we present a case of hepatitis B flare due to LAM resistance in a patient with cirrhosis in which off-label tenofovir was the salvage therapy, followed by maintenance with adefovir.

CASE REPORT

A 36 year old man was first seen at our Department in July 2004 for chronic hepatitis B dating back to 1992. He was on therapy with LAM 100 mg/day started in another hospital from March 2003. At the beginning of the therapy HBV-DNA was 1x10^6 cp/ml (Amplicor assay, Roche) and ALT value 4 x u.n.v. At the observation in our Unit HBV-DNA was still undetectable (by Roche Monitor assay) and ALT value normal. A liver biopsy showed presence of cirrhosis, with minimal inflammatory activity (Ishak score: staging 6; grading 3). The patient received the indication to continue lamivudine therapy and perform an HBV-DNA assay every 3 months and abdominal u.s. examination every 6 months. HBV-DNA was still undetectable on September 2005, then the patient was lost to follow-up because he was working out of the country. On November 2006 the patient became jaundiced while on continued lamivudine therapy. At admission in our unit the patient showed ALTx35 u.n.v., total bilirubin 28.6 mg/dl, albu-
min 2.7 g/dl, cholinesterase 2499 IU/ml and PT 57%, HBV-DNA 1.48x10^6 IU/ml.
Anti-HAV, anti-EBV and anti-CMV IgM tested negative; anti-HCV, HCV-RNA and anti-HDV were negative.
He denied alcohol and drug use.
Abdominal ultrasound showed a coarse liver with no focal lesions and an enlarged spleen.
Endoscopy showed F1 aseophageal varices and normal gastric and duodenal mucosa.
By direct sequencing, M204V and L180M pol gene mutations were detected. The procedure for off-label use of tenofovir was activated and a limited supply was obtained.
After the informed consent was obtained, TDF was started at the dose of 300 mg/day in addition to lamivudine.
The Figure 1 reports the time course of HBV-DNA, ALT, bilirubin and PT. HBV-DNA decreased by 1.5 log after 48 hrs; a steady decrement continued in the following weeks, until it became undetectable (by Taqman Roche) after 6 weeks of therapy.
A parallel ALT decrease was observed, together with a rapid improvement in prothrombin time and bilirubin values. After 45 days of therapy, TDF was substituted with adefovir dipivoxil, 10 mg/day.
Thereafter the patient was monitored monthly; after 10 months HBV-DNA was still undetectable and ALT value was normal.

## DISCUSSION

In patients with cirrhosis the presence of lamivudine resistance may cause an ALT flare with disease decompensation and death within 1-6 months [3].
Adefovir dipivoxil is the salvage therapy for lamivudine-resistant patients. However, it should be added on lamivudine treatment as soon as 1 log increase in viremia is detected, in order to maximize its efficacy [2].
In patients who develop clinical manifestations of lamivudine resistance a rapid and potent antiviral action is required to avoid further clinical consequences.
Tenofovir exerted a more rapid and potent antiviral action than adefovir even in patients with high viral load or with lamivudine resistance [5-9].
When viremia declined, a rapid clinical improvement became evident, even in patients with cirrhosis [10-12]. Most of the data were obtained in patients with HIV-HBV coinfection, because tenofovir is part of anti-HIV drug combination. In our patient, HBV-DNA decreased by 1.5 log within 48 hrs, then continued to decrease at a lower rate until it became undetectable. This agrees with a biphasic viral clearance kinetic under TDF [13].

Therapeutical switch from tenofovir to adefovir has been reported in four cases, all of whom presented viral relapse after 2-7 months of ADV therapy [14, 15]. Two of these patients had detectable HBV-DNA at the time of the switch and two had undetectable HBV-DNA using an assay with low detection limit of 2.6 log/copies. None of the patients received combination with lamivudine.

A key difference in our patient was that serum HBV-DNA tested undetectable at the time of the switch using a high sensitivity method. This might have maximized the long term efficacy of ADV. A second point was the maintenance of lamivudine therapy.

Tenofovir is highly active against LAM-resistant HBV and the few data available do not support a better efficacy of the combination with lamivudine [16-18].

In our case, we maintained lamivudine in view of the switch to ADV.

In conclusion, this case highlights that in critically ill patients with HBV flares due to LAM resistance tenofovir is an effective salvage therapy and that switch to ADV plus LAM is feasible after a complete viral suppression is achieved.

The cost of the drugs and local reimbursement policies are important determinants in the choice of antiviral therapy in chronic hepatitis B.

Key words: hepatitis B, lamivudine, tenofovir, viral resistance.
REFERENCES


