Lamivudine treatment for acute severe hepatitis B : report of a case and review of the literature

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Abstract

The oral nucleoside analogue lamivudine has been effectively used in the treatment of chronic hepatitis B. However, there is limited data concerning the efficacy and safety of lamivudine in patients with severe acute or fulminant hepatitis B. We report the use of lamivudine in a young woman with acute HBV infection and fulminant hepatic failure. Following lamivudine treatment, we noticed a prompt clinical, biochemical, serological and virological response as it was seen in the vast majority of, previously reported, cases. Lamivudine treatment was continued until HBsAg was cleared. Our case, as well as previously reported ones, suggests that lamivudine may have a beneficial effect in selected patients with acute severe or fulminant HBV infection. (Acta gastroenterol. belg., **2008**, 71, **30-32**).

Introduction

Hepatitis B virus (HBV) is a DNA virus transmitted predominantly by percutaneous exposure or sexual contact. Acute HBV infection is, in the vast majority of cases, a self-limited disorder. However, in about 1% of patients it leads to fulminant hepatic failure (1). The mortality of fulminant hepatitis B is approximately 70% and liver transplantation remains the only effective treatment (2-4).

The oral nucleoside analogue lamivudine inhibits HBV replication as it suppresses the HBV – polymerase activity. Therefore, lamivudine reduces serum viral titer to low levels in immunocompetent patients with chronic hepatitis B (5). Moreover, lamivudine has been successfully used in patients with chemotherapy induced fulminant reactivation of chronic hepatitis B (6). Finally, it is well known that lamivudine shows an excellent safety profile in decompensated chronic liver disease (7). However, there is limited data concerning the efficacy and safety of lamivudine in patients with severe acute or fulminant hepatitis B.

We report the use of lamivudine in a young woman with acute HBV infection and fulminant hepatic failure. Moreover, we provide a review of the literature on the effectiveness of lamivudine therapy for acute hepatitis B.

Case report

A 35-year old female patient was admitted to our department with a 1 – week history of anorexia, nausea, jaundice and right upper quadrant abdominal discomfort. Her past medical history was unremarkable for liver diseases. She was a blood donor and had a negative examination for HBsAg nine months before admission. Physical examination revealed a well-nourished, jaundiced and conscious woman. There were neither hepatomegalies nor signs of chronic liver disease. The remainder of physical examination was unremarkable, except of a right upper quadrant abdominal discomfort on deep palpation.

On admission, laboratory tests revealed a concentration of total serum bilirubin of 19.7 mg/dl (predominantly conjugated), alanine aminotransferase (ALT) : 1253 IU/L (normal < 40 IU/L), aspartate aminotransferase (AST) : 991 IU/L (normal < 37 IU/L), alkaline phosphatase (ALP) : 233 IU/L (normal < 129 IU/L). The INR was 2.6. Serum levels of urea, creatinine, serum electrolytes, amylase, total protein, electrophoresis, serum concentration of IgG, IgA and IgM, white blood cell count, hemoglobin concentration, platelet count and differential blood cell count were all within normal limits. Ceruloplasmin and alpha-1 antitrypsin concentration were also normal. An abdominal ultrasound revealed no abnormalities of liver size or texture.

Serologic examination for hepatitis A and C were negative. Moreover, there was no serologic evidence for recent infection with cytomegalovirus, Epstein-Barr virus or herpes-virus. However, serologic tests were positive for hepatitis B surface antigen (HBsAg), IgM antibodies to hepatitis B core antigen and hepatitis B e antigen (HBeAg), whereas antibodies to hepatitis delta virus were negative. The serum HBV-DNA levels, detected and quantitated by polymerase chain reaction (PCR), were 5.1×10^6 copies/ml. Chronic liver disease was ruled out by careful evaluation of the patient's history and liver ultrasonography. Therefore, the diagnosis of acute hepatitis B was made and the patient received supportive treatment.

However, the patient's clinical condition deteriorated rapidly with progressive increase in INR and serum bilirubin levels and three days after admission she was in

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Table 1. — **ALT, INR, HBV – DNA, bilirubin levels before and after initiation of lamivudine treatment**

DAY *	ALT (IU/L)	BILIRUBIN (mg/dl)	INR	HBV-DNA (copies/ml)
1	1253	19.7	2.6	5.1×10^6
2	2506	20.4	3.4	n. t.
3**	3804	21.6	4.0	n. t.
4	3013	25.0	4.3	n. t.
5	2100	23.6	4.3	4.0×10^3
6	1300	26.8	3.9	3.4×10^3
7	625	29.2	2.9	n. t.
8	312	28.1	1.6	2.0×10^3
15	60	20.4	1.0	2.1×10^2
60	26	5.6	1.1	< 400
125	28	0.9	1.1	< 400

* Days from the day of admission
** Initiation of lamivudine
ALT : alanine aminotransferase, INR : international normalized ratio, HBV : hepatitis B virus, n.t. not tested.

a state of grade III encephalopathy. At this point, lamivudine treatment at a dose of 100 mg per day was initiated. A rapid improvement of both symptoms and laboratory tests was observed. After one week the patient was completely asymptomatic. Table 1 shows the serum ALT, INR, bilirubin and HBV-DNA levels before and after initiation of lamivudine. Four months after initiation of lamivudine the liver function tests were completely normal, HBsAg and HBeAg were negative, the anti-HBs antibody was positive and lamivudine was stopped.

Discussion

A variety of large randomized controlled studies have confirmed the efficacy of lamivudine in the treatment of chronic hepatitis B (8-12). Moreover, lamivudine has been successfully used for the treatment of acute hepatitis B after orthotopic liver transplantation (13). In most cases, lamivudine is well tolerated and side effects are rare. However, data in the literature concerning the efficacy of lamivudine in immunocompetent patients with *de novo* acute HBV infection are limited.

In fact, no prospective, randomized controlled trials, have been reported so far on the possible role of lamivudine for the treatment of acute hepatitis B. Three case reports showed a beneficial role of lamivudine in fulminant hepatitis B (14-16). Moreover, three small case series concerning a total of 38 patients with severe acute hepatitis B or fulminant hepatic failure due to acute HBV infection treated with lamivudine have been published (17-19). Table 2 shows analytically the reported results. In most cases (33/38, 86.8%), patients had a favorable outcome. Moreover, no adverse effect due to lamivudine treatment in those patients has been reported. A very recent randomized controlled study shows that although lamivudine causes a greater decrease in levels of HBV DNA, it does not cause significantly greater biochemical and clinical improvement as compared to placebo in patients with acute hepatitis B (20). However, this study was not focused on the subset of patients with fulminant hepatic failure and increased HBV-DNA replication.

Our patient met the criteria for HBV - induced fulminant hepatic failure (21). High serum HBV-DNA levels, measured before the administration of lamivudine, indicated ongoing viral replication. We initiated lamivudine treatment as soon as signs of hepatic encephalopathy were observed. Following treatment, we noticed a prompt clinical, biochemical, serological and virological response, as it was seen in the vast majority of, previously reported, cases (17-19). Lamivudine treatment was continued until HBsAg was cleared.

It is well known that uncomplicated, self limited acute HBV infection has an excellent prognosis and requires no treatment. Fulminant hepatic failure occurs in less than 1% of cases (1). However, the mortality of fulminant hepatitis B is extremely high. Orthotopic liver transplantation remains the only therapeutic modality (2-4). This case, as well as previously reported cases, suggests that lamivudine may have a beneficial effect in selected patients with acute severe or fulminant HBV infection. The effectiveness of lamivudine in those cases could be explained by the rapid suppression of viral replication. Therefore, lamivudine may not be indicated in fulminant hepatic failure patients with low or undetectable HBV DNA levels, this due to the already existed increased immune response. On the other hand, the use of interferon might be dangerous as its principal mode of action is the modulation of the immune system. However, an overwhelming immune reaction is believed to be involved in the pathogenesis of fulminant hepatic failure due to HBV infection (22).

Because randomized, controlled studies in the literature are not yet available we cannot rule out the possibility that the favorable outcome in lamivudine treated patients with fulminant HBV infection may be due to

Table 2. — **Results of case series concerning the use of lamivudine in patients with severe acute or fulminant hepatitis due to HBV infection**

Author	Year	Patients (n)	Response (%)	Transplantation (%)	Side effects of lamivudine
Kondili *et al.*	2004	6	6 (100)	0	none
Weiss *et al.*	2004	15	13 (86.6)	2 (13.4)	none
Tilman *et al.*	2006	17	14 (82.4)	3 (17.6)	none
TOTAL		38	33 (86.8)	5 (13.2)	none

spontaneous recovery and not to treatment *per se*. However, an extensive clinical experience in patients with chronic hepatitis B suggests that lamivudine is a safe and well tolerated drug, even in decompensated liver disease (7). Therefore, there is no rationale to withhold this safe drug from patients with acute HBV infection who have evidence of severe liver injury with ongoing increased levels of viral replication and/or impending acute liver failure.

In conclusion, current data suggest that lamivudine treatment may be beneficial in patients with fulminant hepatic failure due to acute HBV infection. However, larger randomized, control studies are needed to confirm the above results and to clarify whether the early use of lamivudine may decrease the requirement for liver transplantation.

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