Experience with Lamivudine Treatment for Severe Acute Hepatitis B

Antonija Verhaz

Clinic for Infectious Diseases, Clinical Center of Banja Luka, Banja Luka, Bosnia and Herzegovina

SUMMARY

Introduction Experience with lamivudine treatment for acute severe hepatitis B is limited. Fulminant hepatitis develops in 1% of immunocompetent patients with acute hepatitis B.

Objective The aim of this study was to evaluate the efficacy of lamivudine in the treatment of severe acute hepatitis B (SAHB) in immunocompetent adult patients.

Methods Between January 2006 and May 2013 at the Clinic for Infectious Diseases Banja Luka, 13 patients with SAHB were treated with lamivudine at a dose of 100 mg per day. All 13 patients fulfilled at least two of three default criteria: 1. hepatic encephalopathy; 2. total bilirubin greater than 210 μmol /L; and 3. severe coagulopathy (international normalized ratio – INR ≥1.5 or prothrombin time – PT <40%). The criteria were defined according to the experiences reported in the study of Schmilovitz-Weiss et al. "Lamivudine treatment for severe acute hepatitis B". Nine patients had a rapid rise in the total bilirubin and decrease of alanine aminotransferase level, which escalated risk for development of fulminant hepatitis.

Results Within 1-6 months, HBsAg was undetectable in 12 of 13 examined patients. Protective anti-HBsAg developed in 10 of them during 2-14 months. Two patients did not develop protective antibodies, but the result of the analysis of PCR HBV DNA was repeatedly negative. Corticosteroids were shortly used in two patients. One patient died four days after starting the therapy. Lamivudine treatment was well tolerated by all patients.

Conclusion Early treatment with lamivudine can reduce the risk of progression to fulminant hepatitis in patients with SAHB.

Keywords: severe acute hepatitis B; lamivudine; treatment

INTRODUCTION

The incidence of acute hepatitis B (AHB) was largely reduced during the last 20 years as the results of vaccination and routine blood donor screening.

Acute hepatitis B virus (HBV) infection may take a severe course, which can eventually lead to fulminant hepatic failure in about 1% of all cases with AHB. Liver transplantation is currently the only therapeutic option to prevent death [1]. Hepatitis B infection is successfully cleared in most patients or becomes chronic in 5-10% of adult patients. In the minority of patients the disease can progress to acute or subacute liver failure, both with high mortality. The subacute form can cause chronic liver disease, pseudo-cirrhosis ("Kartoffel-Leber") or "cirrhosis".

More than 95–99% of adults with acute HBV infection will recover spontaneously and seroconvert to anti-HBs without antiviral therapy. HBV infection can cause severe acute hepatitis which can progress to acute liver failure. Lamivudine may have a beneficial effect in selected patients with acute severe or fulminant HBV infection. Patients with fulminant or severe hepatitis must be evaluated for liver transplantation. These patients may benefit from NA treatment. Support for such a strategy may be found in a small number of reports mainly with lamivudine. The duration of treatment is not established. However, continuation of antiviral therapy for at least 3 months after seroconversion to anti-HBs or at least 12 months after anti-HBe seroconversion without HBsAg loss is recommended [2-5].

Nowadays, the most common mode of transmission of HBV is unsafe sexual contact. Also, illegal drug use, dental and other medical intervention, acupuncture, piercing and tattooing, may pose a risk for HBV infection. Most patients recover with symptomatic treatment. However, when there are signs of severe liver failure, intensive care is advisable to reduce the risk of the disease progression to fulminant or subacute hepatitis and the need for urgent liver transplantation [5, 6, 7].

Lamivudine is an oral nucleoside analogue with potent inhibitory effect on HBV replication, causing chain termination of an RNA-dependent HBV polymerase. Reports that have been published regarding the treatment of severe forms of acute hepatitis B with lamivudine are limited [8, 9, 10].

OBJECTIVE

The aim of the present study was to evaluate the efficacy of lamivudine in the treatment of immunocompetent adults with acute severe hepatitis B (ASHB) at the Clinic for Infectious Diseases, Banja Luka, Bosnia and Hercegovina.

Correspondence to:
Antonija VERHAZ
Clinic for Infectious Diseases
Clinical Center of Banja Luka
12 beba bb, 78000 Banja Luka
Bosnia and Herzegovina
antonija@blic.net

Table 1. Number of registered patients per year with acute hepatitis B in the Republic of Srpska

Acute hepatitis B (per year)	2006	2007	2008	2009	2010	2011	2012	2013
Total number	35	50	54	66	38	54	63	53

Table 2. Baseline characteristics of the patients

Patient	Sex	Age	Mode of transmission of HBV
1	F	34	Sexual contact
2	M	45	Sexual contact
3	F	24	Dental intervention
4	M	29	Exposure to medical procedures
5	M	44	Exposure to medical procedures
6	M	77	Surgical intervention
7	F	45	Sexual contact
8	M	57	Exposure to medical procedures
9	F	52	Sexual contact
10	F	27	Sexual contact
11	M	20	Sexual contact
12	M	37	Sexual contact
13	M	26	Sexual contact

F – female; M – male

METHODS

This study was a retrospective study. In the period of January 2006–May 2013, 13 immunocompetent patients at the Clinic for Infectious Diseases in Banja Luka were diagnosed as ASHB. All patients were previously healthy. Table 1 shows the total number of reported cases of AHB per year by the Epidemiological Service Institute of Public Health of the Republic of Srpska.

The diagnosis of ASHB was based on the appearance of jaundice and other typical symptoms and biochemical and virological findings. Laboratory findings showed elevated levels of aminotransferases (AST, ALT), total bilirubin, prolonged prothrombin time, and detection of serum HBsAg, hepatitis Be antigen (HBeAg), and immunoglobulin M antibody to hepatitis B core antigen (IgM HBcAb). PCR HBV DNA analysis was not done in all patients, due to the unavailability of equipment. Ultrasound examinations were performed looking for the evidence of chronic liver disease. The patients did not use alcohol and were not drug users.

The patients with SAHB had to meet two of the following three criteria: 1. hepatic encephalopathy, 2. total bilirubin greater than 210 μmol/L, and 3. severe coagulopathy (international normalized ratio – INR ≥1.5 or prothrombin time – PT <40%).

The patients were under follow-up during treatment, including the degree of encephalopathy, coagulation values, liver enzymes and bilirubin levels every week for the first month and then monthly. Serological findings, HBsAg, anti-HBs, HBeAg and anti-HBe were checked every month over the next six months, and titers of anti-HBs were tested at 6-12 months. The accepted criteria for defining clinical and serological recovery from acute hepatitis B was the loss of surface antigen (HBsAg) and the detection of antibodies against HBsAg (anti-HBs), with normalization of serum aminotransferases.

RESULTS

The study included eight men and five women, mean age 44.4 (29-77). All patients were previously healthy. The mode of transmission of HBV was predominantly sexual contact (61.5%) (Table 2). All patients fulfilled at least two of the three criteria for SAHB infection. All patients had severe lysis of hepatocytes (high values of ALT), severe coagulopathy and 9 patients had grade 1-4 encephalopathy (Table 3).

Laboratory tests showed elevated levels of aminotransferases, hyperbilirubinemia (mostly direct), and prolonged prothrombin time. Values of ALT were elevated above the upper limit of the normal, ranging 819-8268 IU/L. Decreased aminotransferases combined with the deterioration of prothrombin time usually indicates a decreasing

Table 3. Biochemical and clinical characteristics of the patients

Patient	Total serum bilirubin* (μmol/L)	AST*/ALT* (U/L)	Protrombin time (% of normal)	INR*	Hepatic encephalopathy (grade)**
1	259	944/1462	40	1.68	I
2	374	2224/4320	23.2	2.50	III
3	581	819/940	40	1.68	II
4	191	8052/4512	12.8	4.24	IV
5	91	7686/6964	5.8	7.12	III
6	365	1954/1770	27.9	2.24	I
7	269	1320/1722	39	1.79	0
8	247	2110/2704	5.1	8.0	I
9	349	2101/1931	55	1.36	II
10	266	3228/5436	36	1.88	II
11	388	2979/4314	41	2.0	II
12	444	1516/5789	42	1.51	II
13	227	5970/8268	44	1.53	I

AST – aspartate aminotransferase; ALT – alanine aminotransferase; INR – international normalized ratio

* Normal values of parameters: a) total serum bilirubin: 17.0 μmol/L; b) AST: 38 U/L; c) ALT: 50 U/L; d) INR: 1.15

** Grade: Assessment of the severity of hepatic encephalopathy is based on a semi-quantitative analysis of mental status that was used on the basis of West Haven criteria.

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Table 4. Time of application, duration and effects of lamivudine treatment

Patient	Interval from onset of symptoms to initiation of treatment with lamivudine (days)	Duration of lamivudine treatment (month)	Clinical response (days)	Normalization of biochemical findings (months)
1	10	3	3	3
2	10	2	2	4
3	30	6	3	6
4	13	1	2	2
5	2	Fatal outcome	Fatal outcome	
6	10	4	3	5
7	12	4	3	2
8	7	1.5	4	3
9	11	4	3	2
10	15	5	3	2
11	9	5	2	3
12	16	2	3	2
13	7	5	3	3

function of liver cells and a progression to liver failure [11]. Some patients had a rapid rise of total bilirubin and a concomitant decrease of alanine aminotransferase level, which escalated the risk of the development of fulminant hepatitis B [11].

All blood samples were tested for HBsAg, anti-HBs and anti-HBc IgM by ELISA tests. All patients were serum HBsAg and anti-HBc IgM positive, and 7 patients were HBeAg positive. Tests for IgM antibodies to the hepatitis A virus, and antibodies to the hepatitis C virus were all negative.

Due to the severe clinical forms of acute hepatitis B and the risk of liver failure, we started giving lamivudine within 2-30 days of the onset of the disease at a dose of 100 mg daily after obtaining informed consent of the patient or family. We gave lamivudine 100 mg orally daily for 1-6 months (Table 4).

Twelve patients responded well to the treatment and their biochemical parameters rapidly improved. In all patients encephalopathy disappeared within three days after starting the lamivudine treatment. Prothrombin time was normalized in all patients within ten days after the administration of lamivudine.

Treatment with lamivudine lasted from 1-6 months, during which the patients' clinical course was monitored, liver function tested, and serological findings obtained. The normalization of aminotransferase and bilirubin values occurred entirely within 2-6 months. One patient died after two days of treatment with lamivudine, related to progression of fulminant hepatitis.

Ten patients lost serum HBsAg and anti-HBs developed in 10/12 (83.3%) (Table 5) a protective titer (in 76.9% seroconversion occurred). Two patients did not develop protective antibodies, but HBV DNA was repeatedly negative. PCR result on several occasions was negative (Table 5). All HBeAg positive patients lost HBe-antigen within six month after starting the treatment and seroconverted to anti HBe and loss of HBeAg within six month from the start of treatment.

Corticosteroids were shortly used in two of 13 patients. One patient with a low PT died of fulminant hepatic failure two days after lamivudine therapy was included. The treatment with lamivudine was well tolerated by all patients.

Table 5. Time of serological seroconversion

Patient	Seroconversion HBsAg/anti-HBs (month)
1	3
2	2
3	6 (without anti HBs)
4	1
5	Fatal outcome
6	4
7	4
8	1.5
9	4
10	5
11	5
12	2
13	4 (without anti HBs)

DISCUSSION

In our study, we administered for a short periods of time lamivudine 100 mg daily (1-6 months) in 13 patients who fulfilled the criteria for acute severe hepatitis B. Lamivudine treatment lasted until the disappearance of HBsAg, or the appearance of protective anti-HBs antibody. Tillman et al. [2] announced that lamivudine treatment led to a rapid recovery with the potential to prevent liver failure and need for liver transplantation. In our patients, there was a rapid clinical, biochemical and serological response, except in one patient who died.

In this regard, Kumar et al. [10] reported that in patients with acute hepatitis B, serum levels of hepatitis B virus DNA fell more rapidly in the lamivudine-treated group than in the placebo-treated group.

According to the literature, patients with acute and severe forms of hepatitis B typically recover from the disease and seroconvert with HBsAg/anti HBs, without liver damage.

It is possible that by using lamivudine in our patients, we obtained a quick biochemical improvement with clinical recovery of the patient, with the elimination of HBsAg. Furthermore, it also reduced the risk of death that can

occur in some patients [12-15]. Unfortunately, there is not much literature on the role of antiviral therapy in SAHB. Many authors have suggested the need for a large placebo-controlled study.

Sometimes, the distinction between a truly SAHB and a reactivation of chronic hepatitis B may be difficult for differential diagnosis and may require liver biopsy. However, nucleoside analogues treatment is the treatment of choice in both cases.

The duration of treatment has not been established. This study is retrospective, with an insufficient number of patients, but, based on our experience, the treatment with lamivudine in patients with severe forms of hepatitis B had a favorable outcome in 12/13 of patients, while patients with fulminant or severe hepatitis must be evaluated for liver transplantation; they may also benefit from oral nucleoside analogues treatment. Support for such a strategy may be found in a small number of reports mainly with lamivudine [9-15]. In the EASL Clinical Practice Guidelines it is recommended that the management of chronic hepatitis B virus infection with the antiviral therapy should continue for at least 3 months after the seroconversion to anti-HBs or at least 12 months after the anti-HBe seroconversion without loss of HBsAg [16].

CONCLUSION

In our study, the treatment with lamivudine led to clinical, biochemical and serological response in immunocompetent patients with severe acute hepatitis B. Patients with fulminant hepatitis are candidates for liver transplantation, which cannot be performed in our country. These patients also may benefit from the treatment with nucleoside analogue. As the majority of our patients, with ASHB recovered under a lamivudine treatment, we can suggest the use of this drug if unable to provide a liver transplantation. Finally, large randomized prospective studies of the effect of lamivudine in severe forms of acute hepatitis B are needed.

REFERENCES

1. Centers for Disease Control and Prevention (CDC). Incidence of acute hepatitis B-United States 1990-2002. Morb Mortal Wkly Rep. 2004; 52(51-52):1252-4.
2. Tillmann HL, Hadem J, Leifeld L, Zachou K, Canbay A, Eisenbach C, et al. Safety and efficacy of lamivudine in patients with severe acute or fulminant hepatitis B, a multicenter experience. J Viral Hepat. 2006; 13(4):256-3.
3. Lee WM. Acute liver failure. N Engl J Med. 1993; 329(25):1862-72.
4. O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology. 1989; 97(2):439-45.
5. European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B. J Hepatol. 2009; 50:227-42.
6. Delić D, Nešić Z, Prostran M, Boričić I, Švirtlih N. Lečenje subakutnog hepatitisa B lamivudinom – pilot studija u Srbiji. Vojnosanit Pregl. 2009; 66(3):199-202.
7. Vučelić B. Hepatitis B – još uvijek najčešće spolno prenosivi hepatitis u Hrvatskoj. Infektološki glasnik. 2010; 30(3):131-4.
8. Kondili LA, Osman H, Mutimer D. The use of lamivudine for patients with acute hepatitis B (a series of cases). J Viral Hepat. 2004; 11:427-31.
9. Schmilovitz-Weiss H, Ben-Ari Z, Sikuler E, Zuckerman E, Sbeit W, Ackerman Z, et al. Lamivudine treatment for acute severe hepatitis B: a pilot study. Liver Int. 2004; 24:547-51.
10. Kumar M, Satapathy S, Monga R, Das K, Hissar S, Pande C, et al. A randomized controlled trial of lamivudine to treat acute hepatitis B. Hepatology. 2007; 45(1):97-101.
11. Santantonio T, Mazzola M, Pastore G. Lamivudine is safe and effective in fulminant hepatitis B. J Hepatol. 1999; 30:551.
12. Roussos A, Koilakou S, Kalafatas I, Kalantzis C, Apostolou N, Grivas E, et al. Lamivudine treatment for acute severe hepatitis B: report of a case and review of the literature. Acta Gastroenterol Belg. 2008; 71(1):30-2.
13. Reshef R, Kaspa RT. Lamivudine in the treatment of acute hepatitis B. N Engl J Med. 2000; 343:1123-4.
14. Roznovský L, Orságová I, Kloudová A, Mrázek J. Lamivudine therapy in patients with severe acute hepatitis B. Klin Mikrobiol Infekc Lek. 2007; 13(2):59-65.
15. Lisotti A, Azzaroli F, Buonfiglioli F, Montagnani M, Alessandrelli F, Mazzella G. Lamivudin treatment for severe acute HBV hepatitis. Int J Med Sci. 2008; 5:309-12.
16. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. J Hepatol. 2012; 57(1):167-85.

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Искуство с ламивудином у лечењу тешких облика акутног хепатитиса Б

Антонија Верхаз

Клиника за инфективне болести, Клинички центар, Бања Лука, Босна и Херцеговина

КРАТАК САДРЖАЈ

Увод Искуство с ламивудином у лечењу тешког акутног хепатитиса Б је ограничено. Фулминантни хепатитис се развија код 1% имунокомпетентних болесника с акутним хепатитисом Б.

Циљ рада Циљ истраживања је био да се процени учинковитост ламивудина у лечењу тешких облика акутног хепатитиса Б код имунокомпетентних одраслих особа.

Методе рада Између јануара 2006. и маја 2013. године у Клиници за инфективне болести у Бањој Луци лечено је 13 болесника с тешким акутним хепатитисом Б применом ламивудина у дози од 100 *mg* дневно. Свих 13 болесника испуњавало је најмање два од три задата критеријума: а) енцефалопатија јетре; б) ниво укупног билирубина већи од 210 *mmol/l*; и в) тешка коагулопатија (*INR*≥1,5 или протромбинско време <40%). Критеријуми су дефинисани у складу с искуствима наведеним у раду Шмиловиц-Вајсове (*Schmilovitz-Weiss*) и сарадника „Ламивудин у лечењу акутног хепатитиса Б". Код девет испитаника утврђени су брз пораст нивоа укупног билирубина и смањење нивоа аланин-аминотрансферазе, који повећавају ризик од развоја фулминантног хепатитиса Б.

Резултати У року од једног месеца до шест месеци, *HBsAg* се није могао измерити код 12 испитаних болесника. Заштитна антитела су се развила код 10 испитаника за 2–14 месеци. Код два болесника заштитна антитела се нису развила, али *HBV* ДНК *PCR* резултат је био у неколико наврата негативан. Кортикостероиди су краткорочно примењени код два болесника. Један болесник је умро четири дана након почетка лечења. Лечење ламивудином добро су подносили сви болесници.

Закључак Рано лечење ламивудином може смањити ризик од развоја фулминантног хепатитиса код болесника с тешким акутним хепатитисом Б.

Кључне речи: тешки акутни хепатитис Б; ламивудин; лечење

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