

Safety and efficacy of lamivudine in patients with severe acute or fulminant hepatitis B, a multicenter experience

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SUMMARY. Acute hepatitis B progresses to liver failure with the need of liver transplantation in about 1% of cases. We treated patients with severe acute or fulminant hepatitis B with lamivudine in an attempt to prevent hepatitis B virus (HBV) reinfection after potential liver transplantation. Since September 2000, 17 patients with severe acute or fulminant HBV infection were treated with 100 or 150 mg lamivudine daily once we had evidence for a severe course as indicated by an INR >2.0. These were compared to a historic control from our unit and to external patients. Fourteen of the 17 patients (82.4%) survived with full recovery without liver transplantation. All these 14 individuals cleared HBsAg on lamivudine within less than 6 months. Twelve patients recovered quickly as indicated by a normalized prothrombin time within 1 week while two patients had a more prolonged course. None of the patients showed an adverse event. Three

patients requiring transplantation despite lamivudine therapy had more advanced disease on admission, of whom one had additionally ingested paracetamol (acetaminophen) while the second was already HBV-DNA negative by polymerase chain reaction on admission. The lamivudine treated patients had significant higher frequency of survival without liver transplantation 82.4 vs 20% (4/20) in the historic control ($P < 0.001$). Similar data were derived from external centres using lamivudine (15/20, 75%). Lamivudine is safe in patients with severe acute or fulminant hepatitis B, leading to fast recovery with the potential to prevent liver failure and liver transplantation when administered early enough.

Keywords: fulminant hepatitis, hepatitis B, lamivudine, severe acute hepatitis, therapy.

INTRODUCTION

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 acute hepatitis B [1]. Liver transplantation is currently the only therapeutic

option to prevent death, which would occur otherwise in approximately 70% of patients [2–6]. Outcome of HBV-induced liver failure is worse than for most other etiologies for acute liver failure as recently reported [6]. No specific therapy is currently established for severe acute hepatitis or fulminant hepatic failure due to HBV infection. Moreover, about 20% of patients transplanted for fulminant hepatitis B suffer from recurrent hepatitis B infection [7]. This rate of recurrence can be reduced by application of hepatitis B immunoglobulin (HBIg) from the time of transplantation [7]. In patients transplanted for chronic hepatitis B it has been shown that the recurrence rate of HBV is further reduced by the combination of HBIg with lamivudine [8]. In case of resistance against lamivudine we would nowadays use adefovir dipivoxil.

For chronic hepatitis B, there are currently three-licensed treatment options: either interferon-alpha, lamivudine or

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Abbreviations: HBV, hepatitis B virus; HBIg, hepatitis B immunoglobulin; ALT, Alanine-aminotransferase; PCR, polymerase chain reaction.

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recently adefovir dipivoxil. While interferon's principal mode of action in chronic hepatitis B is believed to be the modulation of the immune system, nucleoside analogues', as lamivudine, and nucleotide analogues such as adefovir dipivoxil principal mode of action is the inhibition of HBV replication by suppression of the HBV-polymerase activity [9]. Thus in the case of severe acute hepatitis B, interferon may be dangerous as it could accelerate the course to fulminant hepatitis B, where an overwhelming immune reaction is believed to be involved in the pathogenesis [10]. It is even contraindicated in decompensated liver disease [11,12]. In contrast, the oral nucleoside analogue lamivudine inhibits hepatitis B viral replication with a rapid decline of serum HBV-DNA. Importantly, the adverse event rate of lamivudine has been shown to be similar to placebo in patients with chronic hepatitis B [13,14]. In addition, lamivudine showed an excellent safety profile in patients with decompensated liver disease [15].

Furthermore, lamivudine has been used successfully in a few patients with fulminant reactivation of chronic hepatitis B following chemotherapy for tumours that made these patients ineligible for liver transplantation [16–18]. Thus, lamivudine appeared safe in patients with fulminant hepatitis. Taken these safety data, we treated patients with severe acute or fulminant hepatitis B with lamivudine in an attempt to prevent HBV reinfection after potential liver transplantation.

PATIENTS AND METHODS

Definition of severe acute and fulminant hepatitis B

Acute hepatitis B is any sudden onset of liver disease in patients with HBsAg positivity, who have no evidence for a pre-existing liver disease or had tested negative for HBsAg previously (see Fig. 1). We defined severe acute hepatitis B if a further deterioration of liver function occurred indicated by a prothrombin time below or equal to 36% of normal to an INR above 2.0, corresponding and to an absolute prothrombin time ≥ 23 s. Fulminant hepatitis is present if the deterioration of liver function is accompanied by the development of hepatic encephalopathy [19].

Patients

Seventeen patients with a severe acute or fulminant hepatitis B as defined by significant deterioration of prothrombin time (see Fig. 1) were treated with lamivudine 100 or 150 mg/day since September 2000 (Table 1). None of these 17 patients was HDV-positive. One patient intermittently refused medication and thus was excluded from the analysis. The only other patients excluded were patients with HCV or HCV and HIV coinfection both at our and the other centres, two patients with pre-existing liver cirrhosis, and one patient

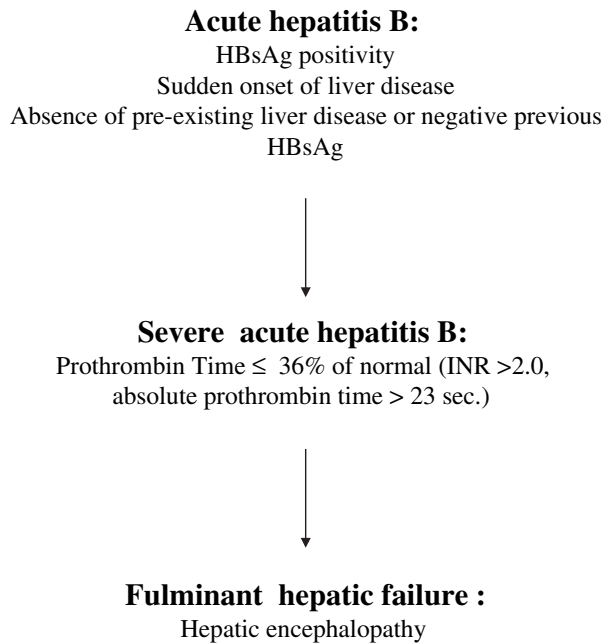


Fig. 1 Definition of different stages of acute hepatitis B. The subsequent stage is indicated by the given definition in addition to all the definitions of the previous stage.

Table 1 Inclusion criteria for patients with severe acute or fulminant hepatitis B

Sudden onset of liver disease, within less than 4 weeks
No apparent pre-existing non-hepatic illness
Absence of any sign of chronic liver disease
HBsAg positivity
INR > 2.0
Encephalopathy*

*Only in case of fulminant hepatitis.

from Larissa was excluded based on an INR of 1.1 (which never deteriorated) indicating absence of severe hepatitis. In addition, one patient, who received lamivudine by mistake only after transplantation early in 2001 was taken into the historic control group.

Initially, the aim of lamivudine treatment was prevention of HBV recurrence in the case of liver transplantation according to our protocol for prevention of HBV-reinfection, where lamivudine is started prior to liver transplantation and continued after liver transplantation in combination with HBIG [8].

Seven of those 17 patients had already hepatic encephalopathy on admission (see Table 1, patients 3, 4, 5, 6, 8, 13, 15), and thus were presenting with fulminant hepatic failure. All 17 but one patient were referred from other hospitals to our tertiary care centre for evaluation of liver transplantation. Baseline characteristics at admission to our

hospital are shown in Table 2. The majority of patients were female (11 of 17), the median age was 34 years (range 20–61), and the probable route of infection was sexual transmission in most cases (see Table 2). Two patients, in addition, had ingested more than 5 g of paracetamol (acetaminophen). One patient was pregnant, but liver disease improved on lamivudine 5 days prior to termination of pregnancy.

Chronic liver disease was ruled out by a careful evaluation of the patients' history and ultrasound of the liver indicating no signs of chronic liver disease. In addition, none of the explanted livers revealed histological signs of chronic hepatitis or cirrhosis. Certainly liver biopsy (or even laparoscopy) and CT or MRI scan would be valuable in ruling out underlying liver disease, this, however, was clinically not indicated. Anti-HBc IgM tested positive in all patients.

Data of lamivudine treated patients were compared to a historical control cohort of consecutive patients treated for severe acute or fulminant hepatitis B but not receiving lamivudine at our centre since 1993 and one patient who by mistake was not treated with lamivudine in early 2001. Identical inclusion criteria were applied (Table 1). Twenty patients were identified of whom two had been HDV positive. All patients tested negative for HCV and HIV antibodies by an ELISA (see Table 4). In addition, data from 20 patients receiving lamivudine for severe acute or fulminant hepatitis derived from five different centres were used as a further control (Table 3).

Clinical and laboratory parameters

Hepatic encephalopathy was graded I–IV as described [20]. Alanine-aminotransferase (ALT) was tested at 20 °C with a normal value below 22 for males and 18 U/L for females. HBV-DNA was tested with the Cobas Amplicor HBV-DNA Monitor™ (Roche Diagnostic Systems, Basle, Switzerland). Viral hepatitis markers were analysed as described earlier [21,22].

RESULTS

Fourteen of the 17 lamivudine-treated patients (82.4%) survived without liver transplantation. Only two patients without improvement of prothrombin time after initiation of lamivudine required liver transplantation and a third patient died from herniation even though stabilization of prothrombin time indicated liver regeneration. One of these had additionally ingested paracetamol (acetaminophen) and showed a prothrombin time being 8% of normal (INR > 8) on admission (see Table 2). The second patient requiring transplantation had been hospitalized with a prothrombin time being 11% of normal (INR > 6) 3 days before referral to our centre and was negative for HBV-DNA by polymerase chain reaction (PCR) on admission. She had progressed to encephalopathy grade IV requiring mechanic ventilation

prior to referral. And the third patient, who died from herniation was admitted without encephalopathy but a prothrombin time being 4% of normal (INR < 10). The later patient had no evidence for encephalopathy on admission thus being considered to suffer from severe acute hepatitis, while the first two had encephalopathy thus being considered to suffer from fulminant hepatitis.

Hepatitis B virus-DNA was detected in 16/17 (94.1%). In 15 patients HBV-DNA could be quantified revealing a mean of 36 million copies/mL with a wide range of 300–464 million copies/mL.

On admission, ALT was elevated at least 30 times above upper limit of normal ranging between 666 and 5161 U/L. All but three patients showed a decline of ALT after start of lamivudine therapy (see Fig. 2a). In some patients ALT levels had started to decline prior to initiation of lamivudine therapy. However, falling aminotransferases in combination with deterioration of prothrombin time usually indicates decreasing liver cell function and progression to liver failure. Importantly, all patients showed deteriorating prothrombin time prior to initiation of lamivudine, but all patients except of the three patients requiring liver transplantation showed an improvement of prothrombin time as a marker for liver function after initiation of lamivudine (see Fig. 2b). Prothrombin time normalized in 12 patients within a week, while in two patients not requiring liver transplantation prothrombin time normalized after more than 2 weeks only. These two patients also showed a prolonged increase in bilirubin, while bilirubin levels declined in the other patients not requiring liver transplantation once lamivudine was initiated or within the first week (see Fig. 2c).

Importantly, no drug related adverse events were obvious and all patients eventually cleared HBsAg on lamivudine within less than 6 months. Lamivudine was given until HBsAg clearance. One of the three patients who progressed to liver failure despite lamivudine lost the HBsAg within 3 days of lamivudine treatment. This enabled liver transplantation without the need of passive immunization with HBIG to prevent HBV-reinfection. Underlining our single-centre experience, only 5/20 patients (25%) from other hospitals who were reported to us included in this analysis needed transplantation.

While 14 of 17 (82.42%) in this case series and 15/20 (75%) lamivudine treated patients from different other hospitals survived without liver transplantation, only 4 of 20 (20%) historical consecutive control patients not receiving lamivudine survived without liver transplantation ($P < 0.001$, see Table 4). All other 16 historic patients progressed to hepatic encephalopathy grades II–IV. This finding remained significant when survival analysis was restricted to those patients without HDV coinfection ($P = 0.001$).

In contrast to low need of liver transplantation in patients being treated with lamivudine, two of three patients who did not receive lamivudine (as lamivudine is still not generally recommended) died or required liver transplantation in one

Table 2 Patients' baseline characteristics at the time of admission to our ICU and initiation of lamivudine therapy at MHH

Sex	Age	ALT (U/L)	ALT (ULN)	Bilirubin ($\mu\text{mol/L}$)	Prothrombin time (%)	INR	Creatinine ($\mu\text{mol/L}$)	Lactate	Grade† of encephalopathy	Source of infection	HBV-DNA ($\times 1000$ cps/mL)	Potential cofactor	Outcome
1	F	30	4680	260	192	3.61	50	n.d.	0	Unknown	320.0		Alive
2	F	25	3887	216	105	2.06	41	2.01	0	Sexual contact	139.0		Alive
3	M	30	5161	235	154	2.40	329	5.32	1	Unknown	32700.0	PCM	Alive
4	F	37	4694	261	67	8.43	113	4.36	1	Sexual contact	185.0	PCM	OLT, alive
5	M	44	1998	91	263	3.45	58	2.2	1	Unknown	207.0		Alive
6	F	21	666	37	444	6.73	50	3.05	4	Sexual contact	<0.2		OLT, alive
7	F	37	3935	219	342	4.25	46	2.99	0	Needle stick	26.5		Alive
8	F	25	1699	94	100	2.40	38	1.31	1	Sexual contact	0.3	Pregnancy	Alive
9	M	52	2440	111	291	5.19	143	5.74	0	Sexual contact	173.0		Alive
10	F	36	4983	277	24	2.27	62	1.28	0	Sexual contact	Positive*		Alive
11	M	20	1797	82	247	3.80	43	4.2	0	Ivdu	10800.0		Alive
12	F	24	2435	135	195	2.06	50	1.61	0	Sexual contact	1750.0		Alive
13	M	61	3910	178	210	5.62	107	3.38	1	Unknown	5.3		Alive
14	F	30	3218	179	248	2.81	49	1.35	0	Sexual contact	21.7		Alive
15	M	19	1706	78	281	3.02	53	2.52	1	Unknown	19.8		Alive
16	F	52	3049	169	393	3.14	56	2.57	0	Unknown	29 400		Alive
17	F	34	2330	129	158	10	76	8.98	0	Unknown	464 000		Herniation, death

F, female; M, male; ALT, Alanine aminotransferase, normal range below 18 and 22 for female and male, respectively; ALT (ULN), times above the upper limit of normal; INR, international normalized ratio for prothrombin time; ivdu, intravenous drug user; PCM, paracetamol (acetaminophen); MHH, Medizinische Hochschule Hannover; ICU, intensive care unit; n.d., not done.

The bold letters indicate the three patients with the worst outcome (two were requiring liver transplantation and one died before transplantation).

*In this patient HBV-DNA was positive (corresponding to more than 3000 cps/mL) but no serum was available for quantification.

†Encephalopathy at admission, where 0 equals severe acute hepatitis, while those with encephalopathy 1 are considered to suffer from fulminant hepatitis.

	Sex	Age	ALT (ULN)	Bilirubin ($\mu\text{mol/L}$)	Prothrombine time (% of normal)	INR	Outcome
1	F	38	255.0	57		8.84	Alive
2	M	69	87.9	414		2.11	Death
3	M	63	47.3	367		3.1	Alive
4	M	40	86.0	87		2.5	Alive
5	F	25	83.0	149		3.45	Alive
6	M	45	127.0	227		1.6	Alive
7	F	41	36.7	377		1.6	Alive
8	F	31	92.3	251		2.01	Alive
9	M	28	59.6	227	52		Alive
10	F	63	38.8	377		4.9	OLT
11	M	21	31.5		32		Alive
12	F	51	65.9	166		1.72	Alive
13	F	38	107.5	117	25	2.79	Alive
14	M	43	60.7	351	46		Alive
15	M	25	89.4	665		2	Alive
16	F	33	58.8	216	6		OLT
17	F	30	30.7	606		2.5	Alive
18	F	39	56.8	96	5		OLT, death
19	F	23	169.5	153		3.5	OLT
20	F	24	77.9	170		2.1	Alive

Table 3 Patients' baseline characteristics at the time of admission to our ICU and initiation of lamivudine therapy at centres other than MHH

F, female; M, male; ALT, Alanine aminotransferase, normal range below 18 and 22 for female and male, respectively; ALT (ULN), times above the upper limit of normal; INR, international normalized ratio for prothrombin time; MHH, Medizinische Hochschule Hannover; ICU, intensive care unit.

The bold letters indicate the five patients with the worst outcome (four were requiring liver transplantation of whom one died, and one died before liver transplantation).

centre in the recent years. Furthermore, the one patient refusing to take lamivudine consistently also deteriorated requiring liver transplantation.

DISCUSSION

Patients with severe acute hepatitis have a rather high chance to progress to liver failure, once severe deterioration of clotting function becomes obvious. In our historical control cohort not receiving lamivudine, the rate of progression to fulminant hepatic failure requiring liver transplantation or leading to death was 80% (16/20). It was not clear whether lamivudine, a well-tolerated antiviral drug [14], may be of benefit for these patients. Based on three case reports showing a benign course of fulminant hepatitis B without adverse events when lamivudine was administered [16–18], we started treating our patients with severe acute hepatitis B with lamivudine to minimize the risk of HBV recurrence after a potential liver transplantation [8]. Surprisingly, most patients in whom we started lamivudine after a diagnosis of severe acute or fulminant hepatitis B was made, recovered within a week without progressing to liver failure and need of liver transplantation. Importantly, we

have seen no adverse events after starting lamivudine. The only patients still requiring liver transplantation despite adequate lamivudine therapy had the most advanced disease on admission as indicated by severely impaired prothrombin time with a prothrombin time being <11 of normal (INR > 6.5). In addition, one of these three patients was already HBV-DNA negative by PCR on admission. In this patient lamivudine was started 3 days after the occurrence of liver failure. One other patient requiring liver transplantation had ingested more than 5 g paracetamol (acetaminophen), which might have contributed to the poor outcome. The third patient was also very advanced with a prothrombin time being 4% of normal (INR of 10). Similarly, most of the patients treated in other centres for severe acute hepatitis B survived without transplantation, and those requiring transplantation had the most advanced diseases.

Altogether these data indicate that early administration of lamivudine is safe and might be beneficial in patients with severe acute or fulminant hepatitis B. This is further supported by a recent report of patients with severe hepatitis B reactivation on chemotherapy also demonstrating a potential benefit of lamivudine. Similarly to our experience, in that report only those patients survived on lamivudine who had

Table 4 Demographics of patients treated with lamivudine and the historic control patients

	Lamivudine treated patients MHH (n = 17)	Historic controls MHH (2) (n = 20)	Lamivudine treated patients outside MHH (3) (n = 20)	Statistical significance (P-value)	
				1 vs 2	2 vs 3
Age (years)	34.2 ± 12.2	31.7 ± 10.9	38.5 ± 14.4	n.s.	n.s.
Sex (F/M)	11/6	13/7	12/8	n.s.	n.s.
HBsAg positive on admission	17	20	20	n.s.	n.s.
HBsAg positive at transplantation	1/2	13/13		n.s.	n.s.
HBcAg positive on admission	5/17	2/19		n.s.	n.s.
Anti-HBs positive on admission	1/15	5/18		n.s.	n.s.
Anti-HBs positive at transplantation	1/2	5/13		n.s.	n.s.
Anti-HBc positive on admission	17	20		n.s.	n.s.
Anti-HBc IgM positive on admission	17	n.d.		n.s.	n.s.
Anti-HBc positive on admission	17	20		n.s.	n.s.
Anti-HBe positive on admission	12/14	19/19		n.s.	n.s.
HDV-coinfection on admission	0/17	2/20	0/20	n.s.	n.s.
HCV-coinfection on admission	0	0	0		
HBV-DNA viral load (million cps/mL)	3.6 ± 9.2	n.a.	n.a.		
ALT (U/L)	3022.7 ± 1562.6	1966.2 ± 1374.3		0.002	
ALT (ULN)	150.4 ± 74.3	89.5 ± 64.4	83.1 ± 52.9	0.18	n.s.
Bilirubin (µmol/L)	247.0 ± 133.7	328.0 ± 206.7	275.8 ± 192.8	n.s.	n.s.
Prothrombin time (INR)	4.15 ± 2.19	3.91 ± 1.59	2.92 ± 1.87	n.s.	n.s.
Creatinine (µmol/L)	79.8 ± 70.3	119.6 ± 119.4	n.a.	n.s.	n.s.
Lactate (µmol/L)	5.1 ± 5.3	5.9 ± 4.9	n.a.	n.s.	n.s.
Progression of hepatic encephalopathy	3/17	11/16*		0.005	
Liver transplantation	2 (11.8%)	13 (61.9%)†	4 (20%)*	0.002	0.01
Death	1 (5.9%)	5 (25%)†	2 (10%)*	n.s.	n.s.
Liver transplantation or death	3 (17.6%)	16 (80%)†	5 (25%)*	0.001	0.001

F, female; M, male; ALT, Alanine aminotransferase, normal range below 18 and 22 for female and male, respectively; ALT (ULN), times above the upper limit of normal; INR, international normalized ratio for prothrombin time; MHH, Medizinische Hochschule Hannover; ICU, intensive care unit; HCV, hepatitis C virus; n.s., not statistically significant; n.a., not available.

The last two columns represent comparisons between historic control (group 2) to actual patients from the MHH (group 1) and actual patients from other clinics (group 3) second last column.

*One patient died prior to OLT, and one died after OLT.

†Three patients died prior to OLT and two died after OLT.

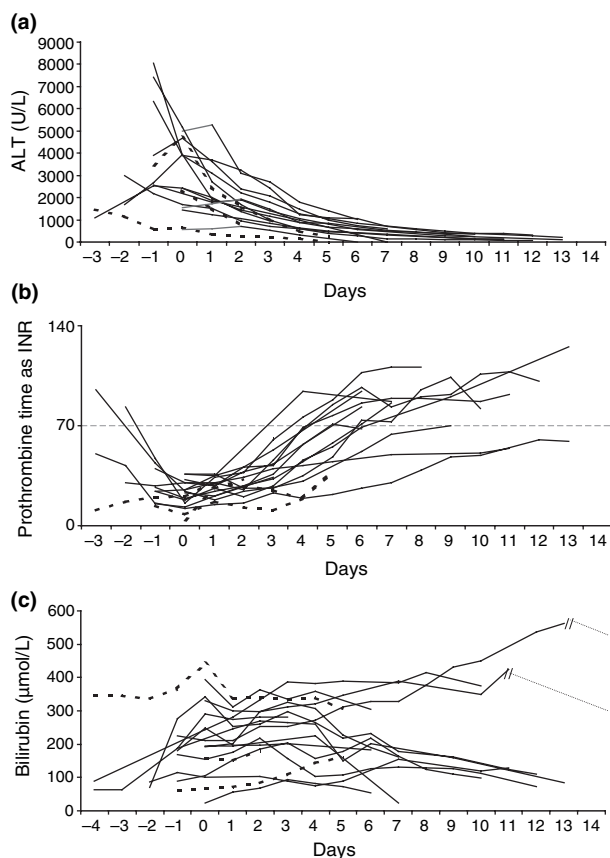


Fig. 2 Individual patients' ALT values in U/L with an upper limit of normal of 22 U/L (a), prothrombin time given as international normalized ratio (b) and bilirubin values in $\mu\text{mol/L}$ (c) in relation to the initiation of lamivudine. The dotted line indicates the patients who progressed to liver failure requiring liver transplantation. // indicates that bilirubin eventually normalized also in these patients. The red lines in 'a' indicate the initial continuation of the increase of ALT in three patients.

less advanced disease when antiviral treatment was started [23].

Currently there have been at least seven cases of patients on chemotherapy with severe hepatitis B reactivation, which did not progress to liver failure on lamivudine [16–18,24,25]. Additionally, it has recently been reported that 5/5 renal transplant recipients with fulminant hepatitis B not receiving lamivudine died while 3/5 similar patients receiving lamivudine survived ($P = 0.083$) [26]. Very recently, a small case series of six patients with acute hepatitis B was reported. In that study, however, only three had severe disease with an INR above 2 [27]. Of these three patients a 58-year-old diabetic died. Even more recently a case series of 15 patients were reported from Israel, showing likewise an immediate improvement of prothrombin time [28]. That report also indicates that late intervention was inefficient. Still, none of the data published so far indicated that an adverse effect might be due to lamivudine in acute, severe acute or fulmi-

nant hepatitis B. Furthermore, in line with our experience that failure to initiate lamivudine is associated with a poor outcome, two recent reports demonstrated fatality or need of liver transplantation when lamivudine is not used [29,30].

Based on this case series of 17 and 20 patients treated with lamivudine for severe acute or fulminant hepatitis B and reported data, we would consider initiating lamivudine therapy once there is evidence for a severe course of hepatitis B (prothrombin time <40% of normal corresponding to an INR equal or higher than 2 or any signs of hepatic encephalopathy), as we would consider those patients at risk for progression to liver failure. Lamivudine treatment should be continued until HBsAg is cleared. In the study under discussion lamivudine was given as part of a protocol to prevent HBV reinfection after potential liver transplantation. Certainly, the use of an historic control has its shortcomings, but taken the immediate improvement of the prothrombin in all patients we consider the data pretty solid, further supported by the recent papers on patients with severe acute hepatitis B. A controlled prospective multicenter trial is warranted. However, given these very promising results, we would not consider a placebo control in the setting of severe acute hepatitis ethically feasible.

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