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Review Article

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Lamivudine Revisited: Long-Term Treatment of Relatively Low-Viremic Hepatitis B Patients on Higher-Dose Lamivudine

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Introduction

Hepatitis B virus (HBV) is a significant global health problem with more than 350 million people chronically infected. Currently it is believed that HBV is responsible for 50% of hepatocellular carcinoma (HCC) worldwide [1-3]. While a cure for HBV is still needed, several oral drugs that suppress viral replication exist. In the United States, six nucleos(t)ide analogues that have been approved at different time periods include lamivudine (1998), adefovir (2002), entecavir (2005), telbivudine (2006), tenofovir disoproxil fumarate (2008) and tenofovir alafenamide (2016).

Lamivudine (LAM) was the first direct-acting antiviral for chronic hepatitis B (CHB) to gain regulatory approvals (1998). In fact, LAM was approved for the treatment of Human Immunodeficiency Virus (HIV) in1995. Soon it was noted that LAM suppressed both HIV and HBV replication in the HIV/HBV co-infected patients. While the LAM dosage for patients with HIV was 300mg daily (150mg twice daily), a dose of 150mg daily was used for CHB patients as off label until Epivir HBV 100 mg was approved in 1998.

In 1996, at the Liver Disease Prevention Center (LDPC) of Thomas Jefferson University Hospital, while participating in the clinical trial with lamivudine 100 mg dose, we began to treat CHB patients with LAM using the 150 mg tablet (Epivir™) licensed for treating HIV infection. This 150 mg dose is higher than the 100 mg dose level that gained worldwide regulatory approvals for treating CHB patients later in 1998. Until adefovir appeared in 2002 as the second anti-HBV drug, the majority of CHB patients were treated with LAM 100mg daily, many of whom had previously failed interferon treatments.

While the use of LAM has fallen out of favor subsequently due to cumulative resistance rates with the approved dosing regimen (100 mg QD), we occasionally used the 150 mg tablets for low-viremic patients, with several practical limitations unique to our patient population especially the financial constraints: newly immigrated from hyper-endemic regions, self-employed with no medical insurance, out of pocket payment for medications. Given that the LAM 150 mg tablet did cost substantially less than 100 mg and far less than newly developed antiviral drugs, we used this dose for such patients.

Here we report long-term results with 150 mg LAM dosing in 27 patients who have continued on the 150 mg daily dose for over 20 years, without the development of resistance or progression of liver disease. The observations reported here may suggest that de novo use of LAM 150mg daily could be revisited as a potential treatment option, particularly in healthcare settings where LAM therapy may be the most cost-effective, easily affordable and only available option.

Below we will first review the history of LAM and its HBV clinical profile from clinical trial data. Then we present our case series of 27 CHB patients who started treatment with LAM 150 mg daily dosing and have continued on LAM 150mg daily for 20 years or longer, without the development of resistance, progression of liver disease or development of HCC.

History of Lamivudine

LAM was initially approved for the treatment of Human Immunodeficiency virus (HIV) in1995. When LAM was found to suppress the HBV replication in the HIV/HBV co-infected patients, this observation subsequently led to Phase 2 and 3 controlled clinical trials that investigated LAM for the treatment of CHB. In the phase 2 trial for CHB patients, LAM was investigated in three doses, 25mg daily, 100mg daily and 300mg daily [4]. A dose of 300 mg daily showed the highest efficacy (serum HBV DNA reduction) during 12 weeks of Phase 2 study. However, the difference between 100mg and 300mg was not statistically significant. Therefore, for the phase 3 trial, LAM 100mg daily was selected. The efficacy of LAM 100mg daily for CHB was well documented in multiple studies [5-11].

LAM has historically been well tolerated with very few side effects, especially compared to interferon. Furthermore, when compared to the newer antiviral therapies, LAM has no renal toxicity or adverse effects on bone mineral density or carcinogenicity in animals. Over the years LAM has become generically available worldwide, and in many global territories it is significantly more affordable than other HBV medications, often including other generically available HBV nucleos(t)ide therapies. In addition to treatment studies in CHB patients, in other HBV trials LAM was known to reduce perinatal HBV infection when given in the last trimester of pregnancy to high-viremic HBV-infected mothers [12]. Also, LAM has been used for prophylaxis or treatment of ALT flares in patients with CHB undergoing chemotherapy or other immunosuppressive treatment [13, 14].

Commencement of Local HBV screening and Initial Use of Lamivudine in 1996

When the first HBV vaccine became available, an HBV prevention campaign was created specifically for immigrants from HBV endemic regions. At LDPC of Thomas Jefferson University Hospital, HBV screening was launched in 1988 for our regional Asian immigrant population. By 1996, more than 25,000 Asian immigrants (the majority from Korea) had been screened for HBsAg and anti-HBs, with 7-10% testing positive for HBsAg. These incidentally identified HBsAg (+) individuals came to LDPC for further evaluation. The evaluation included hepatic function, renal function, CBC with platelets and abdominal ultrasound or magnetic resonance imaging. When the incidentally identified 139 HBsAg (+) individuals were evaluated, 45% were found to have CHB (elevated ALT and abnormal ultrasonic pattern) and 11 % had early cirrhosis (MRI or liver biopsy) [15]. As a large number of HBsAg (+) persons were identified through our screening program again more than half of HBsAg (+) individuals were found to have significant liver disease. Faced with the people identified by HBV screening program and noted to have CHB, treatment for these CHB patients started in 1996 with 150mg tablets of LAM (Epivir™ tablets), as an off label treatment. Simultaneously, LDPC participated in the first phase 3 LAM trials with 100 mg dose and was one of the major participants in this first LAM trial [5]. Over the next ten years, as more antiviral agents became available for the treatment of HBV, LAM (100 mg daily) fell out of favor given cumulative resistance rates [16]. Nonetheless, the resistance rate varied depending on the method used. With the genotypic methods, the resistance rate at 1 year was14% -32%. [17-23]. With the virologic assays, the resistance rate was 6.4% to 15.4% [24-27].

In our experience with LAM 100 mg daily, we observed that the resistance rate was dependent on the baseline DNA level. In patients with HBV DNA $<10^6$ copies/ml (<200,000 IU/ml), the resistance rates at 12 months, 24 months and 36 months were 3%, 9% and 32%, respectively. In contrast, patients with baseline HBV DNNA $>10^6$ copies/ml, the resistance rates were 10%, 36% and 74%, respectively [28].

In the ensuing years, LDPC participated in the multiple clinical studies with newly developed antiviral drugs including adefovir, telbivudine, entecavir (ETV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF). A large portion of our patients including those on LAM 150 mg daily were enrolled in clinical trials discontinued LAM-moved away or were lost follow up. Consequently, we do not have detailed records for those patients. However, we do have records of patients who remained on LAM 150 mg daily and followed up regularly at the LDPC which we have summarized below. Furthermore, as new highly potent antivirals such as TDF, ETV and TAF became available, LAM is no longer the first choice for CHB treatment at our institution. Nevertheless, when patients with newly diagnosed CHB experienced financial difficulties or were without medical insurance, combined with low baseline HBV DNA but with family history of HBV associated HCC and long duration of HBV infection, LAM 150 mg daily was used given its affordability (it was even more affordable than LAM 100 mg daily). This decision was based on our own experience regarding the efficacy and low resistance rate of LAM 150 mg daily for those with low baseline DNA levels [28].

Most recent monthly U.S. wholesale prices (per month) for HBV treatment are as follows: $48 for LAM 150 mg daily, $121 (previously $158 in 2008) for LAM 100 mg daily, $327 (previously $528 in 2008), for adefovir 10 mg daily, $90 (previously $715 in 2008) for ETV 0.5 mg or 1.0 mg daily, $167.18 for TDF 300 mg daily and $1407.11 for TAF 25 mg daily.

A Case Series of 27 Patients Maintained on High-Dose Lamivudine (150 mg Daily)

Reviewing currently active ambulatory patients at the LDPC, we identified 27 patients who continue to do well on LAM 150 mg daily for up to 23 years without development of resistance. These patients were diagnosed at different age (ranging from 12 to 65 years of age) and they began treatment at different time in their disease course. The age at time of diagnosis, family history of HBV, baseline HBV DNA (cp/ml), baseline laboratory data, the year of treatment initiation, time until HBV DNA became undetectable and total number of years treated with LAM are described in Table 1 and 2. Among the 27, one patient at the time of treatment initiation (patient number 4, age 36) presented with established cirrhosis complicated by thrombocytopenia $85x10^3$/ml, HBeAg (-) with HBV DNA level of $3.5x10^5$ copies/ml(the measurement at that time). Another (case 10, age 72) at the time of treatment showed early cirrhosis on MRI.

Treatment initiation was based on the Asian American Guidelines [29]. In this guideline, treatment was indicated when HBV DNA was $>1x10^4$ copies/ml (>2,000 IU/ml) for both HBeAg (+) and HBeAg (-) patients with ALT >30 IU/ml for male and >19 IU/ml for female. For Cirrhosis, treatment was indicated with detectable serum HBV DNA regardless of ALT level.

For patients whose viral load or ALT levels did not meet the treatment criteria (Table 2), special consideration was given in those with strong family history of HBV and HCC, especially those infected at birth (cases 6, 8,16, 17, 21, 25), early cirrhosis in a 72 years old patient (case 10), immunosuppressive therapy (case 19), cardiac surgery (case 20), and HBV-associated glomerulonephropathy (case 6).

In the table, HBV DNA is expressed in copies/ml as it was used in the early stage of HBV treatment. Earlier expression of HBV DNA in pg/ml was converted to copies/ml. To express HBV DNA levels uniformly, later measurement in unit/ml was also expressed

in copies/ml, with $1x10^6$ copies/ml equivalent to 200,000 units/ml, and -$1x10^a$ copies/ml equivalent to 20,000 IU.ml.

In this cohort, there are 13 males and 14 females. As shown in Table 1, the mean age at the time of diagnosis was 33.6 years with a median age of 30 (ranges 15-65). The latest diagnosis occurred at age 65 (although history suggested that the patient was infected during early childhood). There were varying periods between the time of first diagnosis of CHB and the start of antiviral therapy, ranging 0-46 years with a median of 9 years. As shown in Table 2, the mean time to undetectable HBV DNA after treatment initiation was 5.9 months with a median of 5 months (ranges 3-11 months). Of the patients with positive HBeAg at time of treatment initiation (5 patients), all seroconverted to HBeAg-negative/anti-HBe positive, after 3 months, 5, 6, 7 and 8 years of treatment respectively (Table 2).

As of December 2019, none of the 27 patients had detectable serum HBV DNA, abnormal liver function tests, abnormal imaging or documented resistance. All except one patient (patient number 6) have received uninterrupted treatment courses of LAM 150 mg once daily. Patient number 6 had treatment stopped by her physician when her HBV DNA became undetectable after 5 months of LAM treatment. When her HBV DNA became elevated within 3 months, she was restarted on LAM 150 mg daily and achieved undetectable HBV DNA after 4 months. She has remained HBV DNA negative for 16 years. Of the 27 patients, 17 had imaging and 15 had repeat imaging during the course of treatment, ranging from a span of 5 months to 17 years, with a mean of 7.3 years and a median of 7 years. With the exception of 1 CT, all patients had either MRI or ultrasound studies. The images were assessed for the presence or absence of steatosis and signs of chronic liver disease by 2 readers using a 5-point Likert scale for both parameters [30, 31]. Only one patient (case 4) qualified as cirrhotic with trophic changes (right lobe and medial segment atrophy and lateral segment and caudate hypertrophy) and mild nodularity on MRI. which was noted at the time of initiation of therapy and not seen to progress. The majority had no radiographic evidence of steatosis (14/17, 82.4%) and all 3 were evident on MRI imaging with no change in perceived fat content over time in any of the 15 patients with follow up imaging.

Table 1. Characteristics of Patients with Regard to Age at Diagnosis, Family History, Baseline HBV DNA Level, Response Rate and Years on Lamivudine

Patient	Gender	Age	Sex	Age at Dx	Age at Trreatment	Yrs btw Dx & Tx	FHx of HBV	HBeAg/ Anti-HBe	HBV DNA (cp/ mL) at Treatment	Time to DNA (-)	Years on lamivudine
1	M	43	M	27	27	0	Yes	+/-	$2.8x10^6$	3 mos	15
2	M	62	M	38	46	8	No	-/+	$3.4x10^5$	6 mos	16
3	F	58	F	28	45	17	Yes	-/+	$2.8x10^5$	3 mos	12
4	M	55	M	33	36	3	No	+/-	$3.4x10^5$	6 mos	19
5	M	49	M	30	36	6	Yes	-/+	$1.7x10^9$	10 mos	12
6	F	66F	F	30	50	20	Yes	-/+	$4.8x10^2$	4 mos	16
7	M	50	M	17	33	16	Yes	-/+	$7.3x10^5$	6 mos	17
8	F	42	F	30	34	2	Yes	+/-	$6.6x10^3$	9 mos	8
9	F	72	F	65	65	0	Yes	-/+	$5.2x10^7$	4 mos	7
10	M	83	M	62	72	10	Yes	-/+	$1.8x10^3$	3 mos	10
11	M	76	M	43	53	10	No	-/+	$5.0x10^6$	5 mos	23
12	M	46	M	25	40	15	Yes	-/+	$5.8x10^5$	3 mos	6
13	F	48	F	12	38	26	Yes	-/+	$5.5x10^4$	3 mos	10
14	M	61	M	44	44	0	Yes	-/+	$6.9x10^4$	6 mos	17
15	F	56	F	24	46	9	Yes	-/+	$1.8x10^4$	4 mos	11
16	M	56	M	23	42	19	Yes	-/+	$2.0x10^3$	3 mos	14
17	M	64	M	29	46	13	Yes	+/-	$7.66x10^2$	7 mos	18
18	F	42	F	24	30	6	No	-/+	$2.4x10^8$	4 mos	12
19	F	57	F	26	51	25	Yes	-/+	$1.0x10^3$	5 mos	7
20	M	69	M	55	59	4	Yes	-/+	$8.9x10^2$	3 mos	10
21	F	44	F	18	34	16	Yes	-/+	$6.0x10^2$	7 mos	10
22	F	70	F	15	61	46	Yes	-/+	$2.7x10^4$	4 mos	9
23	F	78	F	49	58	9	Yes	-/+	$2.8x10^8$	11 mos	20
24	F	73	F	60	66	6	Yes	-/+	$1.6x10^4$	5 mos	7
25	M	51	M	22	38	16	Yes	+/-	$1.5x10^3$	10 mos	13
26	F	44	F	25	33	7	Yes	-/+	$1.4x10^6$	5 mos	11
27	F	69	M	54	58	4	Yes	-/+	$5.5x10^4$	3 mos	11

Table 2. Baseline HBV DNA, Liver Function, Platelets, Time to Become Negative HBV DNA, and HBeAg Seroconversion

	Age at Treatment	Sex	HBeAg/ Anti-HBe	HBV DNA (cp/ mL)	Serum albumin (g/dl)	Total Bilirubin	ALT	Platelets (x10^3)	Date of Tx	Time to HBV DNA (-) (months)	HBeAg seroconversion	Months or years to conversion
1	27	M	+/-	$2.8x10^6$	4.8	1.0	48	203	6/11/04	3	10/23/09	5 yrs
2	46	M	-/+	$3.4x10^5$	4.9	0.7	49	231	10/13/03	6	None	
3	45	F	-/+	$2.8x10^5$	4.3	0.6	153	132	6/13/07	3	None	
4	36*	M	-/+	$3.4x10^5$	3.2	3.8	536	85	9/18/00	6	None	
5	36	M	+/-	$1.7x10^9$	4.5	0.6	63	276	4/21/06	10	8/9/13	7 yrs
6	50	F	-/+	$4.8x10^2$	2.2	0.1	41	152	9/5/03	4	None	
7	33	M	-/+	$7.3x10^5$	4.7	0.4	31	128	6/11/02	6	None	
8	34	F	+/-	$6.6x10^3$	4.2	0.8	43	185	6/1/11	9	9/16/11	3 mos
9	65	F	-/+	$5.2x10^7$	3.5	3.5	1131	200	7/16/12	4	None	
10	72 #	M	-/+	$1.8x10^3$	4.4	1.0	35	279	8/15/08	3	None	
11	53	M	-/+	$5.0x10^6$	3.9	1.1	161	172	5/24/96	5	None	
12	40	M	-/+	$5.8x10^5$	4.8	1.6	34	154	8/2/13	3	None	
13	38	F	-/+	$5.5x10^4$	4.3	0.4	28	300	8/14/09	3	-/-	
14	44	M	-/+	$6.9x10^4$	4.4	0.9	19	183	5/6/02	6	None	
15	46	F	-/+	$1.8x10^4$	4.7	0.7	11	187	8/12/09	4	None	
16	42	M	-/+	$2.0x10^3$	5.0	0.7	44	211	11/10/05	3	-/-	
17	46	M	+/-	$7.66x10^2$	4.7	1.2	499	116	5/20/02	7	11/8/00	8 yrs
18	30	F	-/+	$2.4x10^8$	4.4	9.9	229	189	5/2/07	4	None	
19	51	F	-/+	$1.0x10^3$	4.9	1.0	78	220	12/28/12	5	None	
20	59	M	-/+	$8.9x10^2$	4.0	0.9	78	152	4/19/10	3	None	
21	34	F	-/+	$6.0x10^2$	4.6	0.7	15	178	10/19/09	7	None	
22	61	F	-/+	$2.7x10^4$	4.8	0.7	26	186	4/5/10	4	None	
23	58	F	-/+	$2.8x10^8$	4.2	0.4	31	218	8/18/99	11	None	
24	66	F	-/+	$1.6x10^4$	4.7	0.7	11	171	5/30/12	5	None	
25	38	M	+/-	$1.5x10^3$	4.5	0.8	16	310	6/12/06	10	12/14/12	6 yrs
26	33	F	-/+	$1.4x10^6$	4.6	0.8	72	216	4/12/08	5	None	
27	58	F	-/+	$5.5x10^4$	4.6	0.8	23	143	4/21/08	3	None	

* Cirrhosis (compensated)
# early cirrhotic feature on MRI (mild atrophy of medical segment of the liver)
$1x10^6$ copies/ml =200,000 IU/ml; $1x10^5$/ml=20,000 IU/ml

Of the 27 patients, 23 had a family history of HBV infection. Nevertheless, the occasion that led to the diagnosis of HBV were varied and as follows: 13 were diagnosed on a routine examination, 5 after a family member was diagnosed with CHB, 3 after reporting symptoms of fatigue, 2 on premedication screening, 2 during blood donation, and 2 during prenatal screening. (Table 3)

Table 3: Occasions Leading to HBV Diagnosis

Occasion Leading to HBV Diagnosis	Number of Patients
Routine	13
Family member sick with CHB	5
Fatigue	3
For other medicine	2
Blood donation	2
Prenatal	2
Total	27

The interval between diagnosis of HBV and the start of antiviral treatment ranged from 0-46 years with a median of 14 years. Sixteen patients started treatment between 0-10 years after diagnosis while 11 patients started treatment between 11- 46 years after diagnosis. These 27 patients have continued LAM therapy for 6-23 years with a median of 12 years and a mean 17.9 years. Nine patients have been on LAM therapy for 6-10 years and 18 patients on LAM therapy for 11-23 years (Table 4).

Table 4: Number of Years on Lamivudine Treatment

Years on lamivudine	Number of Patients
6-10	9
11-23	18

Conclusion

We present this case series of 27 patients with CHB treated with LAM 150mg daily and followed at the LDPC for over 20 years. With some exceptions, the 27 patients were generally low-viremic at the start of treatment, but 17 of the 22 HBeAg-negative patients and 2 of the 5 HBeAg-positive met current Asian American Guidelines treatment thresholds based on HBV DNA levels (>2,000 IU/mL for HBeAg-positive and >2,000 IU/mL for HBeAg-negative patients). They have remained on LAM 150 mg daily for up to 23 years without documented development of resistance. All 27 patients have been evaluated in the clinic within the last 12 months.

Overall, these patients not only experienced improved liver function and successful viral suppression, but also demonstrated reversal of early cirrhosis (on imaging and labs, case 4,10) with no progression of liver disease and no development of HCC. This case series suggests that LAM 150 mg daily may lead to lower rates of resistance as compared to the traditional dose of LAM 100 mg daily, at least in relatively low-viremic patients. Given the lack of resistance development, safer side effect profile and improved cost-effectiveness in many global territories, we suggest that the 150 mg daily dose of LAM be re-visited as an effective and safe treatment option for patients with CHB, in particular, those with low baseline HBV DNA, financial limitations and good compliance.

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