Original Article

Liver histological reversibility of lamivudine in treatment-naïve children with chronic hepatitis B: a retrospective cohort study from a single center Shanghai China

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Background: Low viral load of hepatitis B virus (HBV) infection may also result in serious liver complications. Whether long-term suppression of HBV replication has beneficial effects on the reversibility of the liver histology associated with chronic hepatitis B (CHB) in children is unclear. This study assessed the histological response of lamivudine (LAM) in CHB children.

Methods: Treatment-naïve CHB patients who 1≤ aged <18 years, indicating the immune-active phase, and receiving LAM were enrolled. Demographics, biochemical value, virology and histology, and safety were retrospectively analysed. Patients visit the hospital at baseline, every 12 weeks during treatment, and every 24 or 48 weeks after treatment withdrawal. Histological inflammatory improvement was defined as a ≥1-point decrease in the inflammatory score. Fibrosis regression was defined as a decrease of ≥1 point or no worsening of the fibrosis score.

Results: Total 35 children enrolled, 13 of them were lost, and 22 patients remained in the study up to 10 years after treatment. Liver biopsy results both at baseline and before treatment withdrawal were available for 14 of the 22 patients. Of the 14 children, 78.6% were male and 78.6% were HBeAg-positive. At baseline, the mean age was 7.3±5.2 years. The serum HBV DNA level of 13 subjects was 7.3±1.3 $\log_{10}$ IU/m. and alanine aminotransferase (ALT) was 142±102 U/L. The mean inflammation score was 2.9±0.7. The mean fibrosis score was 3.7±0.8. The mean duration was 96.0±23.6 weeks (median 96 weeks). All patients (100%) had a normal ALT after a median 12-week treatment; after 24-week, HBV DNA were <1,000 IU/mL in 92.9%. At a median of 30-week, 100% of the HBeAg-positive patients showed HBeAg seroconversion; 7.1% exhibited HBsAg seroconversion after 24-week treatment. After a mean of 96-week, the 14 patients (100%) exhibited a mean 2.2-point inflammatory improvement from baseline (P<0.001), and 92.9% exhibited a mean 2.1-point fibrosis reduction (P<0.001). No virological breakthroughs or serious adverse events occurred.

Conclusions: This study showed that 96-week mean duration of LAM may reverse advanced inflammation and fibrosis/cirrhosis in young CHB children.

Keywords: Children; chronic hepatitis B (CHB); lamivudine monotherapy (LAM monotherapy); inflammation improvement; fibrosis reversibility

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Introduction

Over 350 million people are estimated suffering from chronic hepatitis B (CHB) virus infection worldwide (1). Persistent replication of hepatitis B virus (HBV) is associated with higher risk of developing liver-related mortality, such as cirrhosis, and hepatocellular carcinoma (HCC), especially when HBV DNA levels are high (2,3). Therefore, the primary aim of antiviral treatment is to suppress HBV replication persistently (4-7).

Interferon-α (IFN-α), lamivudine (LAM), adefovir (ADV), entecavir (ETV), and tenofovir (TDF) has been approved for the antiviral treatment of CHB in children by American Food and Drug Administration (FDA) (8,9). However, each drug has its own limitation for pediatric CHB because of the developmental characteristics. LAM, the first oral pyrimidine nucleoside analog, suppresses HBV replication by viral reverse transcriptase inhibition; which is reported that it can improve liver histology and normalize liver enzyme. But LAM is not recommended as a first-line drug because of its high rate of drug resistance (9). Two studies of LAM treatment for one and three years reported the slowing of clinical liver disease progression in adult patients with advanced fibrosis and cirrhosis (10,11). A meta-analysis showed that TDF was superior in alanine aminotransferase (ALT) normalization, HBV DNA reduction HBeAg-negative conversion rate, safety, and total bilirubin levels than ADV in patients with CHB. But when ADV was combined with LAM or ETV, they often showed the same antiviral efficacy as TDF in regarding ALT level and Tbil level, and combined therapy can reduce adverse reactions effectively (12). However, low HBV viral load may also result in serious liver complications. Persistent liver injury leads to healing and scar tissue formation, which resulting in fibrosis and eventually cirrhosis. Fibrosis or cirrhosis occurs through activated hepatic stellate cells secreting fibrillar collagens (13-15). LAM may reverse liver fibrosis/cirrhosis by the inhibition of stellate cells secreting collagen fibers.

Whether long-term suppression of HBV replication has beneficial effects on the reversibility of the liver histological inflammation and advanced fibrosis associated with chronic HBV infection in children is unclear. The study reports here the effects and safety of a mean 96 weeks of LAM-induced viral suppression on the serological response and histological features related to liver inflammation and fibrosis or cirrhosis in children, using evaluable histology obtained at baseline and before treatment withdrawal retrospectively. We present this article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-496/rc).

Highlight box

Key findings

- After a mean 96-week of lamivudine treatment, the 14 patients (100%) exhibited a mean 2.2-point inflammatory improvement from baseline (P<0.001), and 92.9% exhibited a mean 2.1-point fibrosis reduction (P<0.001).

What is known and what is new?

- Low viral load of HBV infection can also result in serious liver complications.
- Mean 96-week duration of lamivudine may reverse advanced inflammation and fibrosis/cirrhosis in young children with chronic hepatitis B, which is safe.

What is the implication, and what should change now?

- Lamivudine could be considered in children with chronic hepatitis B aged <2 years old, who had interferon alpha contraindications.

Methods

This retrospective study was performed in Children's Hospital of Fudan University, Shanghai, China. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Children's Hospital of Fudan University, Shanghai, China (No. 2021-51). Written inform consent is obtained from each child's parent(s). Demographical, biochemical, virological and histological data as well as adverse event assessments of the children treated with LAM were analysed.

Inclusion and exclusion criteria

Inclusion criteria: (I) treatment-naïve patients aged ≥1 year and <18 years were eligible if they were HBsAg-positive; (II) children with 2× ULN ≤ ALT ≤10× ULN, HBeAg-positive subjects with HBV DNA ≥20,000 IU/mL or HBeAg-negative subjects with HBV DNA ≥2,000 IU/mL, histological inflammation grading ≥2 or fibrosis staging ≥2 for at least 6 months, indicating the immune-active phase; (III) children with CHB receiving antiviral monotherapy with LAM after their parents provided informed consent.

Exclusion criteria: (I) patients testing positive for hepatitis A, C, D or E or for HIV, having a history or evidence of chronic liver disease other than CHB, or were

suspected of having HCC; (II) patients with a history of significant chronic pulmonary, cardiac, or renal disease, thyroid disease or diabetes, immunodeficiency disease, previous solid organ or stem-cell transplant, or evidence or history of malignancy; (III) other definitive liver diseases.

Treatment and follow-up

The LAM dose was 3 mg/kg·d daily (max dose of 100 mg daily).

Serum hepatitis B e antigen (HBeAg), hepatitis B s antigen (HBsAg), hepatitis B e antibody (HBeAb), hepatitis B s antibody (HBsAb) (measured by enzyme-linked immunosorbent assays) and HBV DNA [measured by real-time quantitative PCR (qPCR); limit of detection, <1,000 IU/mL before 2019, <500 IU/mL since 2019] were measured at baseline and every 12 weeks during treatment, every 8 weeks until week 24, and every 24 or 48 weeks after treatment withdrawal. The HBV genotype was identified by HBV surface antigen phylogenic analysis.

Clinical, laboratory, and adverse event assessments were performed every 4 weeks until week 12, every 12 weeks thereafter during treatment, every 8 weeks until week 24, and every 24 weeks during follow-up after treatment withdrawal. The assessments included standard haematology, coagulation function, alpha-fetoprotein (AFP), and liver ultrasonographic or computed tomographic scans.

Liver biopsy samples were collected from all children at baseline within 6 months before treatment initiation, a second biopsy was taken before LAM withdrawal according to the children's or parents' willingness (mean 96 weeks). One independent pathologist examined all biopsy slides, and the timing of biopsy and treatment assignment were concealed for the baseline and (mean) week 96 samples. The biopsy slides were scored for inflammation and fibrosis using the Metavir (16) systems.

Changes in histological inflammation and fibrosis/cirrhosis from baseline up to week 96 were analysed for available pooled data with the Metavir scoring. Histological inflammatory improvement was defined as a ≥1-point decrease in the inflammatory score. Fibrosis regression was defined as a decrease of at least 1 point or no worsening of the fibrosis score.

Efficacy included the biochemical response, which was defined as alanine aminotransferase (ALT) normalization, and the virological response, which was defined as the proportions of patients with plasma HBV DNA loads lower than the detection limit. Serological endpoints included serum HBeAg loss and seroconversion (HBeAg-positive patients) and HBsAg loss and seroconversion.

Safety and tolerability were regularly evaluated, including serious adverse events associated with treatment discontinuation, HCC or death.

Statistical analysis

Clinical and demographic characteristics of the patients were assessed at baseline. Virological, biochemical and serological data were matched regarding time (±12 weeks) with the corresponding baseline data and those before withdrawal. Quantitative variables across groups were compared with the Wilcoxon rank sum test and qualitative variables with Fisher's exact test. Changes in histological inflammation and fibrosis scores were assessed with the sign test. Missing data was processed by using the method of average replacement. All P values were 2-sided, with $P<0.05$ considered statistically significant. All analyses and graph generation were performed by using SPSS (version 22) and GraphPad Prism (version 7).

Results

Demographics and baseline characteristics

Of 35 children enrolled and treated with LAM, all had evaluable liver biopsy samples at baseline before treatment. But 13 patients were off study for loss. And the other 22 patients remained in the study up to 10 years after treatment. Liver biopsy results both at baseline and before treatment withdrawal were available for 14 of the 22 patients (63.6%) (mean week 96); no secondary biopsy before withdrawal was available for the remaining 8 (36.4%) patients, mainly because their parents had refused the procedure. Histological inflammation and fibrosis scores were available at baseline for all 22 patients and at both timepoints (first biopsy at baseline; secondary biopsy before withdrawal, mean 96 weeks) for 14 (*Figure 1*). Overall, the 14 children with biopsies at both timepoints and treated with 96-week LAM monotherapy were included in the analysis.

None of the 14 treatment-naïve subjects treated with LAM monotherapy had obvious symptoms; 78.6% (11/14) were male. The mothers of all the subjects were positive for HBsAg (100%), as based on information obtained from a detailed history. No patient had a history of blood product transfusion before biopsy. The mean age before treatment was 7.3±5.2 years, ranging from 1-year-1-month to 16-year-6-month (median 6.9 years, interquartile range 1.9–11.0 years). Up to 78.6% (11/14) of the subjects were

HBeAg positive, 21.4% were HBeAg negative, before treatment. All children were HBsAg-positive (100%). Among the 11 subjects in whom HBV genotype assessment was performed, the distribution of genotypes was narrow (B: 18.2%, 2/11; C: 81.8%, 9/11; no other genotypes).

At the time of treatment initiation, 13 subjects (92.9%) were HBV DNA positive; 1 case was transient HBV DNA undetectable. The mean serum HBV DNA level of the 13 detectable subjects was 7.3±1.3 $\log_{10}$ IU/mL. The mean serum ALT level was 142±102 U/L (range, 10–397 U/L).

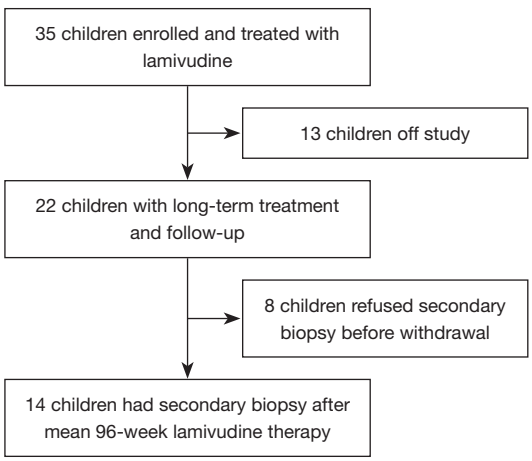

Figure 1 Flowchart summarizing the composition of histology cohort.

The degree of liver inflammation ranged from none to severe inflammation; fibrosis stage ranged from none to cirrhosis. Before treatment, no inflammation was detected in any child (score 0); in contrast, mild inflammation was seen in 7.1% (score 1, 1/14), moderate inflammation in 78.6% (score 2, 7.1%, 1/14; score 3, 71.4%, 10/14), and severe inflammation in 14.3% (score 4, 2/14). The mean inflammation score was 2.9±0.7.

At baseline, no fibrosis was observed in any of the patients (score 0), though mild fibrosis was seen in 7.1% (score 1, 1/14), moderate fibrosis in 7.1% (score 2, 0%, 0/14; score 3, 7.1%, 1/14), and cirrhosis in 85.8% (score 4, 12/14). The mean fibrosis score was 3.7±0.8.

The mean duration of LAM therapy was 96.0±23.6 weeks (median 96 weeks, range 48–172 weeks).

The baseline characteristics are summarized in *Table 1*.

Biochemical and virological response

Before treatment withdrawal, the proportion of patients

Table 1 Baseline characteristics (n=14)

Patient No.	Gender	Liver biopsy		HBV genotype	Age	Duration of lamivudine, weeks	Follow-up period
		Grade	Stage				
1	M	2	1	–	7 y 2 m	80	8 y 1 m
2	M	3	4	–	16 y 6 m	100	7 y
3	M	3	4	C	9 y 2 m	48	7 y
4	M	3	4	–	1 y 5 m	104	2 y 8 m
5	M	3	4	C	14 y 8 m	92	2 y
6	M	4	3	B	6 y 3 m	76	7 y 7 m
7	M	4	4	B	1 y 1 m	100	7 y
8	M	3	4	C	12 y 2 m	80	2 y
9	M	3	4	C	1 y 1 m	100	3 y 5 m
10	F	1	4	C	2 y 9 m	100	4 y 1 m
11	F	3	4	C	6 y 7 m	128	5 y 8 m
12	M	3	4	C	10 y 8 m	144	3 y
13	F	3	4	C	10 y 8 m	92	5 y 11 m
14	M	3	4	C	2 y	72	5 y 6 m

M, male; F, female; HBV, hepatitis B virus; y, year; m, month; "–", no testing.

Table 2 Response to lamivudine therapy

Response	Baseline	Treated	P value
Age (months)	87.6±62.4	–	–
Duration of lamivudine (weeks)	96.0±23.6	–	–
Follow-up period (years)	4.8±2.0	–	–
ALT (U/L)	142±102	12.2±5.3	<0.001
HBV DNA (log_{10} IU/mL)	7.3±1.3	Undetectable	<0.001
Liver biopsy (point)			
Grade	2.9±0.7	0.7±0.6	<0.001
Stage	3.7±0.8	1.6±1.3	<0.001

Data are shown as mean ± standard deviation. ALT, alanine aminotransferase; HBV, hepatitis B virus.

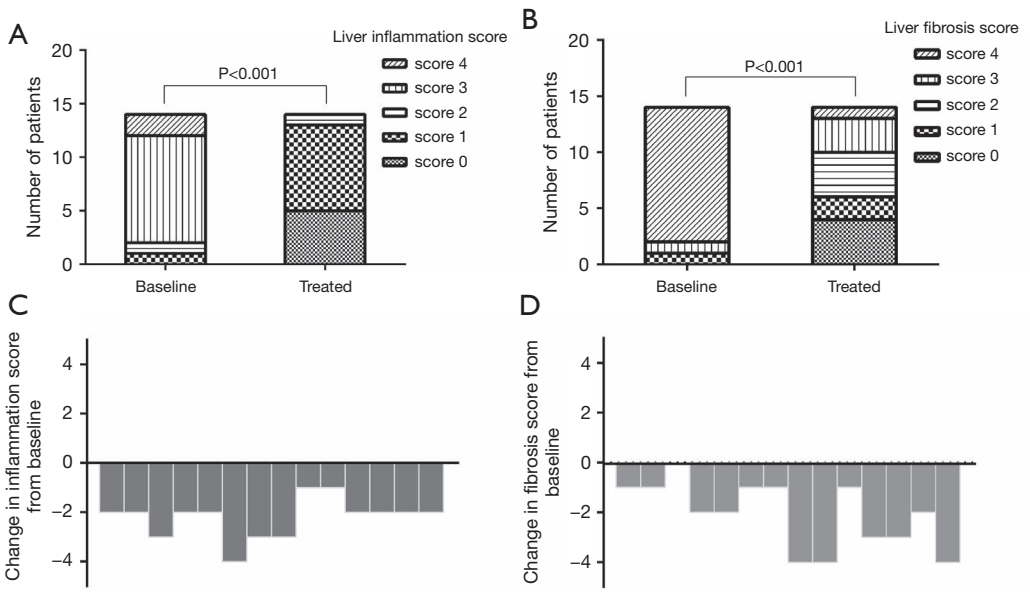

Figure 2 Histological changes after lamivudine treatment (n=14). (A) The proportion with mild or no inflammation (score 0–1) increased from 7.1% (1/14) at baseline to 92.9% (13/14) at week 96 (P<0.001). (B) The distribution of fibrosis scores also indicated improvement after therapy as indicated by a progressive increase in the proportion with mild disease and decreases in the proportion with severe disease (P<0.001). (C) Regression of inflammatory improvement was documented in 100% (14/14) of patients after a mean 96 weeks of treatment. (D) Thirteen of the 14 patients (92.9%) exhibited >1-point improvement of fibrosis score after treatment, and the mean change from baseline in the fibrosis score was a 2.1-point reduction after treatment.

with normal ALT level was 100% (14/14) at a median of 12 weeks of treatment. Similarly, 100% of the patients (14/14) had an HBV DNA level <1,000 IU/mL at a median of 24 weeks of LAM treatment (*Table 2*). In addition, 100% of HBeAg-positive patients (11/11) experienced HBeAg loss and seroconversion at a median of 30 weeks of therapy, and maintained sustained seroconversion during follow-up. One patient (7.1%, 1/14) showed HBsAg loss and seroconversion at 24 weeks of therapy and maintained sustained seroconversion during the 5-year follow-up after drug withdrawal.

Genotypic testing for resistance was not performed because all of the patients achieved good virological and biochemical responses (HBV DNA <1,000 IU/mL and ALT ≤1× ULN). Moreover, no virological breakthrough occurred during treatment.

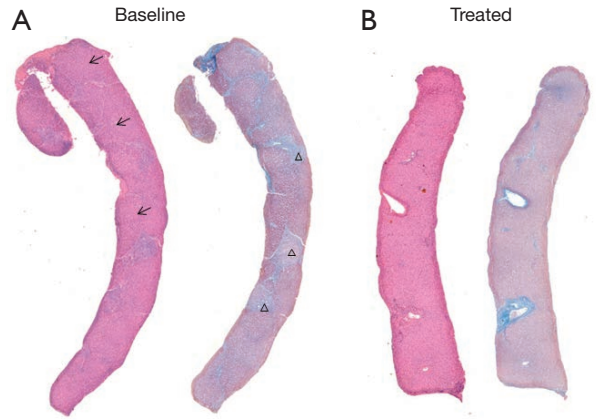

Figure 3 Liver biopsy samples stained with Masson's trichrome and demonstrating a reduction in inflammation and cirrhosis after 96-week lamivudine therapy in a 1-year-1-month-old, HBeAg-positive, HBV genotype C boy. (A) The baseline biopsy sample showed an inflammatory score of 3 and fibrosis score of 4, which indicated severe inflammation (↙) and cirrhosis (△). (B) After 96 weeks treatment with lamivudine, the 2-year biopsy sample showed both inflammatory score and fibrosis score of 0, which indicated no inflammation or fibrosis. HBeAg, hepatitis B e antigen; HBV, hepatitis B virus.

Histological response

After a mean 96-week treatment with LAM, all 14 patients (100%, 14/14) showed histological inflammatory improvement; biopsies both at baseline and before withdrawal were available for all. The mean change in inflammatory score from baseline was a 2.2-point reduction after 96 weeks of treatment (*Figure 2*). Thirteen of the 14 patients (92.9%) exhibited ≥1-point improvement of fibrosis score after treatment, and the mean change from baseline in the fibrosis score was a 2.1-point reduction after treatment. One of the 14 patients did not show a reduction in fibrosis score from baseline to after 102 weeks of LAM treatment, with a score of 4 at both baseline and before withdrawal. This patient had viral suppression (undetectable HBV DNA) and normal serum ALT level before treatment withdrawal. However, the inflammatory score improved from 3 at baseline to 0 at the time of withdrawal. *Figure 2* shows the changes in the distributions of inflammatory and fibrosis scores at baseline, and after the mean 96-week treatment.

After the mean 96 weeks of LAM therapy, the proportion of patients with inflammation decreased (*Figure 2A*,*2C*). The proportion with mild or no inflammation (score 0–1) increased from 7.1% (1/14) at baseline to 92.9% (13/14) at week 96 (P<0.001). The distribution of fibrosis scores also indicated improvement after LAM therapy as indicated by a progressive increase in the proportion with mild disease and decreases in the proportion with severe disease (P<0.001) (*Figure 2B*,*2D*). At baseline, 7.1% (1/14) of patients had no or mild fibrosis (score 0–1); this proportion was 42.9% (6/14) at week 96. Similarly, 7.1% (1/14) had moderate fibrosis scores of 2 and 3 (pronounced bridging fibrosis to cirrhosis) at baseline, but this ratio increased to 50% (7/14) at a mean of 96 weeks. Overall, regression of fibrosis was documented in 92.9% (13/14) of patients and histological inflammatory improvement in 100% (14/14) of patients after a mean 96 weeks of LAM treatment. Furthermore, patients with the most severe liver injury showed the greatest extent of improvement (*Table 2*, *Figure 2*). Viral suppression was documented in 13 (92.9%) of the 14 patients after a mean 96-week therapy for whom the measurement was available.

Twelve of the 14 patients displayed advanced fibrosis or cirrhosis at the baseline. With mean 96-week LAM therapy, 11 of them showed ≥1-point fibrosis score reduction, with a median reduction of 2.2 points from the baseline. Biopsy samples of a 1-year-and-1-month-old HBeAg-positive boy are showed in *Figure 3*, carrying HBV genotype C. The baseline biopsy sample had an inflammatory score of 3 and a fibrosis score of 4, indicating severe inflammation and cirrhosis. After 96 weeks of treatment with LAM, the biopsy sample had both an inflammatory score and a fibrosis score of 0, which indicated no inflammation or fibrosis.

Safety

LAM treatment was well tolerated, and LAM treatment was not discontinued in any patient because of an adverse event. Three patients (21.4%, 3/14) experienced on-treatment ALT flares, and all of these cases were resolved with continued treatment. None experienced treatment-related serious adverse events, and no severely abnormal results in other laboratory assessments were observed.

Follow-up

The median follow-up period was 4.8±2.0 years, and the longest follow-up lasted for 8 years and 1 month (*Tables 1*,*2*).

Two of the patients were lost after withdrawal. One child could not visit our hospital for >18 years of age after 2 months of therapy withdrawal. The other 11 children

maintained a normal ALT level during the follow-up. Two of them (18.2%, 2/11) experienced HBV DNA breakthrough after treatment withdrawal (cases 6 and 8). Five cases (45.4%, 5/11) were transiently HBV DNA positive during follow-up (cases 1, 3, 7, 10 and 11), whereas four (36.4%, 4/11) had sustained HBV DNA negativity during the follow-up period (cases 4, 9, 13 and 14). There was no significant difference in treatment duration for these children ($P>0.05$).

All HBeAg-positive patients (100%, 11/11) had HBeAg loss and seroconversion at a median of 30 weeks of therapy and maintained sustained seroconversion during follow-up. One patient (7.1%, 1/14) exhibited HBsAg loss and seroconversion at 24 weeks of therapy, and had maintained sustained seroconversion when assessed during the 5-year follow-up after withdrawal.

No child was found to have signs of HCC during follow-up performed at the time of the most recent visit.

Discussion

The aim of antiviral treatment for CHB is to suppress viral replication maximally, control liver fibrosis and prevent clinical complications associated with hepatic decompensation and HCC (4-7). However, there is little evidence available on the effect of long-term HBV suppression on liver histology, especially in children. This current study of long-term follow-up summarizes the efficacy and safety of LAM monotherapy on liver inflammation and fibrosis/cirrhosis in treatment-naïve, HBeAg-positive and HBeAg-negative children with CHB. After exposure to LAM monotherapy of median 96 weeks, histological inflammatory improvement and regression of fibrosis/cirrhosis were 100% and 92.9%, respectively. Overall, the treatment is safe and effective. No HCC was detected during treatment or follow-up. These histological analyses extend the clinical efficacy of LAM therapy at a mean of 96 weeks in children with advanced fibrosis or cirrhosis in real-world. Therefore, the treatment responses observed from this study are broadly applicable.

Viral suppression below the level of PCR assay detection occurred in all patients, and all also had a normal serum ALT level at the time before withdrawal and had maintained normal ALT levels when assessed during follow-up. Because of the maintained viral suppression, no evidence of virological rebound or genotypic resistance to LAM was observed during treatment in the current study. However, after treatment withdrawal, 18.2% of the children had HBV DNA breakthrough, 45.4% were transiently HBV DNA positive, and 36.4% were sustained HBV DNA negative during the follow-up period. There was no significant difference between the treatment duration of these children. All of the paediatric patients (100%) experienced HBeAg loss and seroconversion at a median of 30 weeks of LAM monotherapy, with sustained seroconversion during follow-up. In addition, 7.1% of the patients experienced HBsAg loss and seroconversion at 24 weeks of therapy and had maintained seroconversion when assessed during the 5-year follow-up after drug withdrawal. These results were similar to previous reports of studies performed in both adults and children (10,11,17,18). In children with two histological assessments, those who did not show HBeAg seroconversion or HBsAg loss/seroconversion also experienced improvement of inflammation and reversal of fibrosis in liver histology during long-term treatment. It suggested that liver histology improvement was more closely associated with viral suppression than immunological response.

Treatment of chronic HBV infection with LAM, an old polymerase/reverse transcriptase inhibitor, could reverse advanced fibrosis or cirrhosis in small subsets of adult patients. However, it is accepted that LAM results high drug resistance of 20–75% because of incomplete virological suppression in adult patients in the long-term, leading to poor clinical outcomes (10,11,19-21). Longer-term histological data of LAM from nucleoside-naïve patients with CHB exists (11). In general, antiviral drug resistance of LAM affects the histological benefits negatively. Another study of 3 years of LAM therapy revealed slowing of liver disease progression in adult patients with advanced fibrosis and cirrhosis (10). However, disease progression was not assessed histologically, and serum HBV DNA levels were not reported in that landmark study. Although LAM is the first nucleoside agent for the treatment of children aged ≥1 year with CHB approved by the US FDA. It is not recommended as a first-line drug for antiviral treatment in patients with CHB due to high resistance (4-7). This study of 14 patients with sequential histology data obtained over 96 weeks included 12 patients with cirrhosis at baseline. Nearly all patients on LAM had viral suppression after a mean of 96 weeks of treatment, which was associated with inflammation improvement in 100% and fibrosis/cirrhosis regression in 92.9%. One of the limitations is that this study did not assess drug resistance because all the patients achieved good virological and biochemical responses and no virological breakthroughs occurred in our group.

The histological response of fibrosis regression is probably due to viral suppression achieved with long-term LAM treatment in this study. Maintenance of viral suppression is feasible given the overall favourable safety profile in clinical practice. Reversibility of fibrosis or cirrhosis would be expected to translate into clinical benefits, as previously studies shown (10,11). In one study, HCC incidence was lower in advanced fibrosis patients treated with LAM than placebo, which could be offset by the higher drug resistance rates over time to a certain extent (10). In this study, the low rate of serious liver complications, such as HCC, was consistent with sustained viral suppression. Indeed, viral suppression occurred in most children (92.9%), and all patients had a normal serum ALT level at the time of the week-96 biopsy. Because of the maintained viral suppression, and no virological rebound was observed in the current study, which suggesting these patients were at minimal risk for antiviral drug resistance. All patients (100%) had HBeAg seroconversion at a median 30 weeks on LAM treatment. In addition, 7.1% of children had HBsAg loss and seroconversion at 24 weeks of therapy. Of course, one of the limitations is that the sample size was small, and a larger sample and long-term detailed follow-up are needed.

Conclusions

In conclusion, treatment with LAM for an average of 96 weeks maintains viral suppression in treatment-naïve children with CHB. No virological breakthroughs or serious adverse events occurred. The findings draw attention to the regression of liver inflammation and fibrosis/cirrhosis in children with CHB when long-term viral suppression is achieved. LAM may be considered in children with CHB aged ≤2 years old, who had interferon alpha contraindications.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-22-496/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-22-496/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-22-496/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Children's Hospital of Fudan University, Shanghai, China (No. 2021-51). Written informed consent is obtained from each child's parent(s).

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