Research Article
Viral Hepatitis

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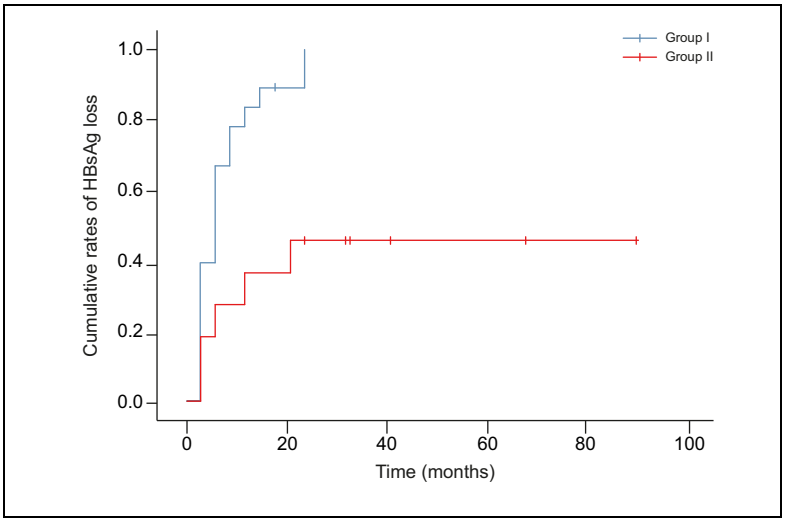
Early initiation of antiviral therapy contributes to a rapid and significant loss of serum HBsAg in infantile-onset hepatitis B

Graphical abstract



Highlights

- Infantile hepatitis B is an unusual yet serious condition which has scarcely been studied.
- No treatment options are proposed for infantile hepatitis B by expert panel consensuses or clinical practice guidelines.
- Early initiation of lamivudine can lead to a significant loss of serum HBsAg in infants with ALT $\geq 2\times$ upper limit of normal.

Authors

Shishu Zhu, Yi Dong, Limin Wang, Weiwei Liu, Pan Zhao

Correspondence

doczhaopan@126.com
(P. Zhao)

Lay summary

Chronicity is a serious threat to infants infected with hepatitis B. However, no treatment measure has been recommended for infantile-onset hepatitis B in current guidelines. In order to evaluate the benefit and safety of antiviral therapy in infantile-onset hepatitis B, a real-world cohort study was conducted. Long-term follow-up results showed that early initiation of antiviral therapy with lamivudine safely led to a rapid and significant loss of serum hepatitis B surface antigen in the present subset of infants with alanine aminotransferase $\geq 2\times$ upper limit of normal. Further trials with larger cohorts are needed.

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Early initiation of antiviral therapy contributes to a rapid and significant loss of serum HBsAg in infantile-onset hepatitis B

Shishu Zhu[1], Yi Dong[1], Limin Wang[1], Weiwei Liu[2], Pan Zhao[1,3,*]

[1]*The Fifth Medical Center (formerly Beijing 302 Hospital), Chinese PLA General Hospital, Beijing 100039, China;* [2]*Medical Statistics Section, Academy of Military Medical Sciences, Beijing 100850, China;* [3]*The First Affiliated Hospital of Xinxiang Medical University, Weihui, Henan 453100, China*

See Editorial, pages 856–858

Background & Aim: There is a paucity of data regarding antiviral therapy in hepatitis B virus (HBV)-infected infants aged <1 year who have elevated alanine aminotransferase. This study aims to assess the efficacy and safety of antiviral therapy initiated in infancy.

Methods: A real-world cohort study was conducted from January 2010 to December 2017. HBV-infected infants under 1 year of age, with persistent elevation of alanine aminotransferase and high viral load, were recruited and divided into 2 groups. Group I included 18 infants whose parents chose to initiate antiviral therapy with lamivudine before 1 year of age. Group II included 11 infants whose parents chose to initiate antiviral therapy with interferon-α after 1 year of age and not to receive any antiviral therapies before 1 year of age. The main outcome measure was rate of serum HBV surface antigen (HBsAg) loss at month 12 of treatment.

Results: There were no statistical differences between Groups I and II regarding baseline characteristics. No infants in Group II developed spontaneous HBsAg loss before 1 year of age. In Group I, the cumulative rates of HBsAg loss at month 3, 6, 9 and 12 of treatment were 39%, 67%, 78% and 83%, respectively. In Group II, the cumulative rates of HBsAg loss at month 3, 6, 9 and 12 of treatment were 18%, 27%, 27% and 36%, respectively. Statistical differences existed in the cumulative rates of HBsAg loss between the 2 groups (log-rank test, $p = 0.0023$). No serious adverse events occurred in the study.

Conclusion: Early initiation of antiviral therapy for infantile-onset hepatitis B contributes to a rapid and significant loss of HBsAg. Further trials with larger cohorts are needed to verify our results.

Lay summary: Chronicity is a serious threat to infants infected with hepatitis B. However, no treatment measure has been recommended for infantile-onset hepatitis B in current guidelines. In order to evaluate the benefit and safety of antiviral therapy in infantile-onset hepatitis B, a real-world cohort study was conducted. Long-term follow-up results showed that early initiation of antiviral therapy with lamivudine safely led to a rapid and significant loss of serum hepatitis B surface antigen in the present subset of infants with alanine aminotransferase ≥2× upper limit of normal. Further trials with larger cohorts are needed.

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Introduction

Hepatitis B virus (HBV) infection is a global public health problem that causes liver-related morbidity and mortality.[1–3] Despite passive-active immunoprophylaxis using hepatitis B vaccination with or without hepatitis B immunoglobulin (HBIg), up to 8%–10% of newborns of HBV surface antigen (HBsAg)-positive mothers still acquire HBV infection.[4] Most infected infants acquire HBV infection asymptomatically during perinatal period and have normal alanine aminotransferase (ALT) levels; however, some cases may present with onset hepatitis with elevated ALT.[5] As an unusual yet serious condition, infantile-onset hepatitis B after neonatal immunoprophylaxis has scarcely been studied.

Previous reports showed that chronic infection was most likely to develop in children under 6 years of age, with an overall prevalence of 30%–50% rising to 80%–90% if they were infected as infants.[6] Chronicity becomes a serious threat to HBV-infected infants. However, according to current guidelines, no antivirals have been recommended for the population. In view of the low therapeutic coverage when current treatment recommendations are followed and the worrisome consequences of HBV infection becoming chronic, more specialists argue that every measure should be considered to prevent progression of pediatric HBV infection.[6,7] As a classical antiviral drug, lamivudine (LAM) has been shown to be safe and effective in human immunodeficiency virus (HIV)-infected infants and in preventing mother-to-infant transmission of HBV or HIV infection.[8–12] Therefore, we designed the present study to assess the efficacy and safety of LAM for the treatment of infantile-onset hepatitis B.

Patients and methods

Study population

This is a real-world prospective cohort study. From January, 2010 to December 2017, we enrolled consecutive infants under 1 year of age who fulfilled the following criteria: presence of

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* Corresponding author. Addresses: The Fifth Medical Center (formerly Beijing 302 Hospital), Chinese PLA General Hospital, No. 100 of West Fourth Ring Middle Road, Beijing 100039, China, or The First Affiliated Hospital of Xinxiang Medical University, No. 88 of Jiankang Road, Weihui, Henan 453100, China. Tel.: +86 10 66933464; fax: +86 10 66933020 (P. Zhao).
E-mail addresses: doczhaopan@126.com, zhaopan302@sina.com (P. Zhao).

HBsAg in serum, serum HBV DNA ≥10^5 IU/ml, persistent elevation of ALT (≥2× upper limit of normal (ULN, 40 IU/L)) without jaundice and no evidence of other comorbidities. A frank conversation was held with the parents of each infant about the benefits and risks, both known and unknown of the antiviral treatments prior to the beginning of the study. Finally, 18 families chose to receive antiviral therapy with LAM before 1 year of age (Group I); 11 families chose to initiate antiviral therapy with interferon (IFN) after 1 year of age (Group II) and infants in this group were given no antiviral drugs before 1 year of age. For Group II, reevaluation of indications for antiviral therapy was performed before treatment initiation. Written informed consent was obtained from each infant's parents before the beginning of the study. The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethics committees of the Fifth Medical Center (*formerly* Beijing 302 Hospital) of Chinese PLA General Hospital.

Treatment regimen

Infants in Group I received LAM monotherapy (4 mg/kg, daily[9,11]); IFN (3 MU/m^2 to 5 MU/m^2, qod) could be added to those who did not clear HBsAg after 1 year of age.

Infants in Group II were initially treated with IFN monotherapy (3 MU/m^2 to 5 MU/m^2, qod). LAM (4 mg/kg, daily) was added to those who had a decline in serum HBV DNA of <2$\log_{10}$ (by PCR, Roche COBAS® AmpliPrep, lower limit of detection: 20 IU/ml) after 3 months of IFN monotherapy.

The main outcome measure was rate of serum HBsAg loss at month 12 of treatment. Antiviral therapy should be terminated in cases of HBsAg seroconversion (disappearance of HBsAg and presence of anti-HBs) with undetectable HBV DNA. After 12 months of treatment, infants who did not develop HBsAg seroconversion continued their therapies until HBsAg seroconversion or HBV e antigen (HBeAg) seroconversion (disappearance of HBeAg and presence of anti-HBe) occurs.[3] Fig. 1 shows the flow diagram of the study.

Clinical monitoring

Infants were monitored every 3 months. Viral profile (HBsAg quantification (by Roche COBAS HBsAgII-Q, lower limit of detection: 0.05 IU/ml), anti-HBs, HBeAg, anti-HBe, HBV DNA) and liver function tests were routinely carried out at each visit and infants were clinically evaluated for any adverse effects. The HBV reverse-transcriptase gene was sequenced in infants with clinically suspected LAM resistance. The detailed sequencing procedure was provided in our previous paper.[13]

Statistical analysis

Data analyses were performed using SAS 9.2 software (SAS Institute Inc, Cary, NC, USA). Continuous data were expressed as mean ± standard deviation. Categorical data were expressed as the number of subjects or percentages. Group comparisons were performed using the Wilcoxon rank sum test or *t* test for continuous variables, and the Chi-square test or Fisher's exact test for categorical variables. Kaplan-Meier method was used to calculate the cumulative rates of HBsAg loss and differences were determined using the log-rank test. Tests were two-sided and a *p* value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 29 infants were eventually included. All mothers of the infants had positive serum HBsAg and HBeAg and high levels of HBV DNA, and were treatment-naive. All infants were administered with HBV vaccine at birth. Of these infants, 18 (11 boys and 7 girls) were in Group I and 11 (10 boys and 1 girls) were in Group II. There were no statistical differences between Group I and Group II with respect to the characteristics at baseline (Table 1).

Twelve infants in Group I and all infants in Group II underwent liver biopsy before therapy. Grade of inflammation and stage of fibrosis in liver histology were evaluated according to Scheuer's criteria.[14] Fig. 2 depicts the distribution of grade of inflammation and stage of fibrosis between Group I and Group II. G2 and S1 predominated in each group. No statistical differences were found across the 2 groups with respect to grade of inflammation ($p = 1.0000$) or stage of fibrosis ($p = 0.4606$).

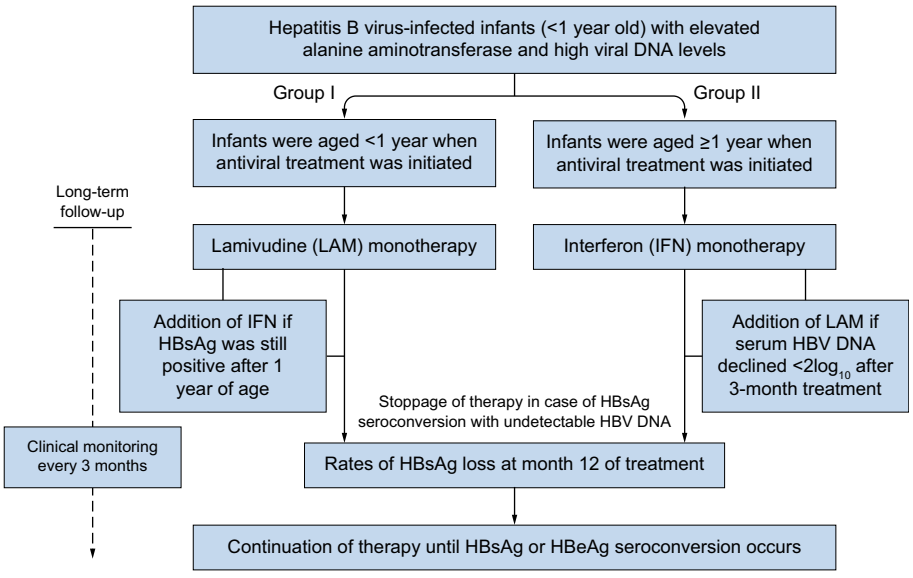

Fig. 1. Flow diagram of the study. HBeAg, HBV e antigen, HBsAg, HBV surface antigen; HBV, hepatitis B virus; IFN, interferon; LAM, lamivudine.

Table 1. Baseline characteristics of HBV-infected infants enrolled in the study.

Parameters	Group I (n = 18)	Group II (n = 11)	*p* value
Sex (boys/girls)	11/7	10/1	0.1096
ALT (U/L)	357 ± 303	209 ± 117	0.1775
HBV DNA (log_{10} IU/ml)	7.55 ± 1.06	7.78 ± 1.09	0.5146
HBsAg quantification (log_{10} IU/ml)	4.28 ± 0.70	4.25 ± 0.58	0.8974
HBeAg status			
Positive	17	10	1.0000
Negative	1	1	
HBV genotype			
B	2	0	0.5123
C	16	11	
Immunoprophylaxis with hepatitis B immunoglobulin			
Yes	10	7	0.7167
No	8	4	
Breastfeeding			
Yes	9	8	0.2732
No	9	3	
Birthweight (g)	3,468.3 ± 237.8	3,484.6 ± 301.2	0.8733
Gestation period (weeks)	39.5 ± 0.9	39.7 ± 1.1	0.5232
Age of diagnosis (months)			
Median (range)	6 (3–10)	7 (5–11)	
Age of commencing treatment (months)			
Median (range)	8 (6–11)	12 (12–24)	
Age of liver biopsy (months)			
Median (range)	8 (6–11)	9 (5–11)	

HBeAg, HBV e antigen, HBsAg, HBV surface antigen; HBV, hepatitis B virus.

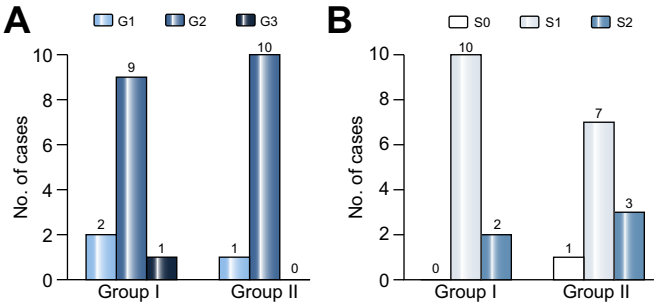

Fig. 2. Distribution of grade of inflammation (Scheuer's criteria) and stage of fibrosis (Scheuer's criteria) in liver histology in Group I and Group II.

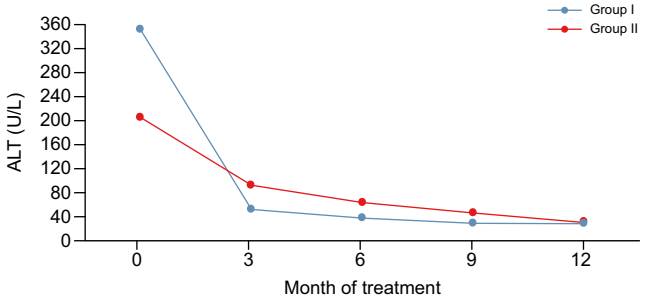

Fig. 3. Changes of mean ALT levels of the infants from baseline to month 12 of treatment in Group I and Group II. ALT, alanine aminotransferase. (This figure appears in colour on the web.)

Treatment response

No infants in Group II developed spontaneous HBsAg loss before 1 year of age; while 9 infants receiving LAM monotherapy in Group I achieved HBsAg loss before 1 year of age. There was a statistically significant difference between the 2 groups ($p = 0.0052$).

All infants in both Group I and Group II had undetectable HBV DNA by month 12 of treatment. The change in mean ALT levels of the infants from baseline to month 12 of treatment is depicted in Fig. 3. In Group I, the cumulative rates of HBsAg loss at month 3, 6, 9 and 12 of treatment were respectively 39% (7/18), 67% (12/18), 78% (14/18) and 83% (15/18). A total of 15 infants developed anti-HBs at month 12 of treatment, 8 of whom developed anti-HBs before month 6. In Group II, the cumulative rates of HBsAg loss at month 3, 6, 9 and 12 of treatment were respectively 18% (2/11), 27% (3/11), 27% (3/11) and 36% (4/11). A total of 3 cases developed anti-HBs at month 12 of treatment, 2 of whom developed anti-HBs before month 6. There were significant differences regarding the rates of HBsAg loss between the 2 groups at month 12 of treatment ($p = 0.0169$).

Long-term follow-up

During follow-up after 12-month treatment, 2 additional infants in Group I lost HBsAg, while no additional cases in Group II developed HBsAg loss. The median duration of treatment in Group I and Group II was respectively 6 months and 12 months. Eventually, all infants except 1 (18 in Group I, 10 in Group II) achieved HBsAg or HBeAg seroconversion in the study and accordingly ended their antiviral therapies. These cases have been followed for a median of 102 months (range 17 to 105) since off-treatment. No seroconversion occurred during off-treatment period and no relapse has been observed to date. Overall, a total of 17 infants achieved HBsAg seroconversion and 1 developed HBeAg seroconversion in Group I; a total of 4 infants achieved HBsAg seroconversion and 6 developed HBeAg seroconversion in Group II. Fig. 4 shows the cumulative rates of HBsAg loss from the beginning of the study. Significant differences existed between Group I and Group II ($p = 0.0023$). Group I had higher rates of HBsAg loss and HBsAg decreased more rapidly.

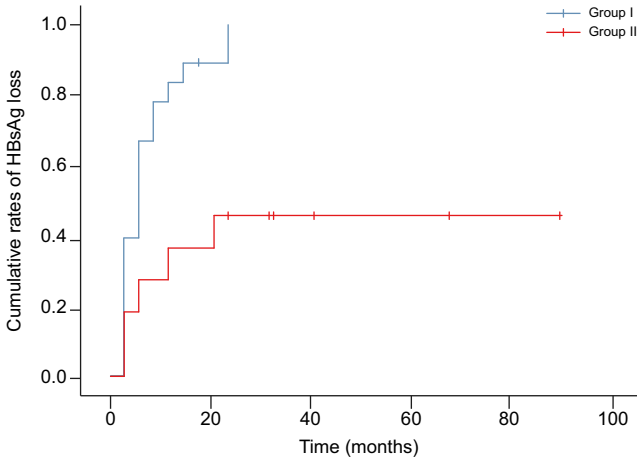

Fig. 4. Cumulative rates of serum HBsAg loss from the beginning of the study. Differences were determined using the log-rank test ($p = 0.0023$). HBsAg, hepatitis B virus surface antigen. (This figure appears in colour on the web.)

Table 2. Cumulative adverse events in the study.

Adverse events	Group I (n = 18)	Group II (n = 11)
Fever	4	9
Neutropenia	3	7
Decreased appetite	2	7
Rash	1	0
Febrile convulsion	0	1

One patient who was initially treated with IFN at 22 months of age in Group II discontinued his therapy at month 9 of treatment due to febrile convulsion. His serum HBV DNA became undetectable at the time. Then the patient switched to entecavir monotherapy from IFN and LAM combination therapy and is still on treatment to date. His serum HBV DNA remains undetectable at the latest clinical visit, but HBeAg seroconversion has not been achieved.

No serious adverse events were observed in the study. Fever was the most common adverse event (4 in Group I; 9 in Group II). Subsequently, neutropenia developed in 10 cases (3 in Group I; 7 in Group II), decreased appetite in 9 (2 in Group I; 7 in Group II), febrile convulsion in 1 (in Group II) and rash in 1 (in Group I). All reported adverse events are listed in Table 2. No adverse events were found among the infants who were treated with LAM alone. Virological breakthrough or LAM resistance did not occur in the study.

Discussion

The uncertainties regarding the natural history of HBV infection in children make development of guidelines for management of pediatric patients very complex.[5] In an expert panel consensus from the United States and the sole clinical practice guideline from Europe,[15,16] no treatment options are proposed for HBV-infected children younger than 1 year old. Low therapeutic coverage exacerbated by restrictive treatment guidelines may facilitate disease progression in these patients. Additionally, few large trials of antiviral therapy in children exist to guide treatment decisions.[17] The conundrums often put physicians into a dilemma in real-world clinical practice.

It is reported that the rate of spontaneous HBsAg clearance in Asians with vertically transmitted HBV is extremely low, between 0.5% and 1.4%.[18] However, there is little published data that describes changes in HBV status in infancy. One study that investigated the outcome of infantile hepatitis B showed that 7 in 20 cases with non-fulminant hepatitis developed chronic infection.[5] In the present study, no infants in Group II before 1 year of age (as no-treatment control) developed spontaneous HBsAg loss. Therefore, in view of the high rate of chronicity and its associated worrisome consequences, antiviral treatments in HBV-infected infants with elevated ALT levels and high viral load should be considered.

Timing of treatment is a critical decision in order to maximize therapeutic benefit.[19] In the present study, infants who initiated their antiviral therapies before 1 year of age (Group I) obtained more benefits than those who initiated therapies after 1 year of age (Group II). Infants in Group I had higher rate of HBsAg loss, shorter treatment duration and lower incidence of adverse events. Though the majority of cases in Group II developed HBeAg seroconversion, it is not an ideal goal for pediatric patients because negative HBeAg usually represents a still progressive and difficult-to-cure phase.[20]

In the study, no LAM resistance was observed. Reasons for this may be associated with the short treatment course in the majority of infants who achieved early cessation of therapy and the combination with IFN in some cases.[21] Nevertheless, considering that LAM has not been widely used in many parts of the world because of its low-barrier to drug resistance, application of high-barrier-to-resistance antivirals in the special population can be further studied.

A strength of our study is the well characterized cohort which provides new evidence for the optimal management of younger HBV-infected infants. Nevertheless, it also has the limitation of sample size. There is a need for further larger scale studies to validate the results, which may facilitate the improvement of current guidelines.

In conclusion, early initiation of antiviral therapy can lead to a rapid and significant loss of HBsAg in HBV-infected infants with persistent elevation of ALT (≥2× ULN) under 1 year of age. Further trials with larger cohorts are needed to verify our results. To the best of our knowledge, this is the first report regarding antiviral therapy for infantile-onset hepatitis B.

Financial support

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Pan Zhao contributed to the design of the study. Shishu Zhu, Pan Zhao, Yi Dong and Limin Wang were responsible for participant recruitment. Shishu Zhu collected the data. Pan Zhao and Wei-

wei Liu analysed the data. Pan Zhao wrote and revised the manuscript. All authors reviewed and approved the final version of the manuscript.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.06.009.

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