Authors' contributions

Both authors contributed to the writing of the paper. All authors gave final approval of this version to be submitted.

Supplementary data

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Author names in bold designate shared co-first authorship

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Antiviral treatment for hepatitis B in infancy: Still an issue for debate

To the Editor:

We read with interest regarding the article "early initiation of antiviral therapy contributes to a rapid and significant loss of serum HBsAg in infantile-onset hepatitis B".[1] The authors used lamivudine to treat 18 infants with positive HBsAg and elevated alanine aminotransferase (ALT) >2x the upper limit of normal (Group 1 in the study), and followed by optional interferon. The cumulative rates of HBsAg loss at month 3, 6, 9, and 12 of treatment were 39%, 67%, 78%, and 83%, respectively. The data are encouraging for early antiviral treatment in infancy. However, we have concerns regarding the clinical features of these infants and whether their hepatitis B is chronic. The authors did not mention if these infants are symptomatic or not, and why did these infants receive liver function tests? Moreover, they did not report whether HBsAg carriage in these infants receiving lamivudine (LAM) treatment lasted longer than 6 months.

The authors mentioned the previously reported high chronicity rate of up to 90% in infants infected with HBV.[2] The high chronicity rate was from those infants acquiring HBV infection from their HBeAg-positive mothers. Such infants have normal liver function, representing a group in the immune-tolerant stage probably due to maternal HBeAg exposure. As a reference, our previous prospective study of children born to highly viremic mothers, 2 of the 13 infants with positive HBsAg at 6 months of age spontaneously became HBsAg negative at 12 months of age, supporting this.[3]

In contrast, the natural course of symptomatic hepatitis B in infancy is different. Our previous study found that 65% (13/20) of the infants with non-fulminant hepatitis B and 73% (8/11) of patients with fulminant hepatitis B spontaneously cleared HBsAg.[4] Therefore, the spontaneous HBsAg and HBeAg seroconversion rate was inherently higher in infants with elevated ALT, compared with infants with normal ALT. Elevated ALT in infancy usually means a lack of immune tolerance or early onset of immune activity. In Zhu *et al.*'s study, 2 infants were HBeAg negative at baseline (Table 1), which may indicate that the infants were in the course of acute HBV infection, with a high chance of spontaneous HBsAg seroconversion. In addition, about 40% of the group 1 patients and 20% of group 2 patients in this study cleared HBsAg within a few months. This observation suggested that the majority of these infants had symptomatic hepatitis B and ran a natural course different from those without ALT elevation.

Based on these results, we do not assume that infants with HBV infection from their mothers necessarily have chronic HBV infection. Those born to HBeAg-positive or HBeAg-negative mothers, with normal or with elevated ALT levels, have a different disease course. Better defined criteria for chronic hepatitis B infants are needed to identify subgroups who really need treatment. Issues regarding when to stop antiviral treatment, as well as treatment-related side effects and drug-resistant viral mutants in young children need to be clarified. Although lamivudine has been used to treat fulminant hepatitis in infancy and severe acute hepatitis B in adults, the efficacy in infants is still controversial due to limited case numbers.[5,6] Well-controlled clinical trials are warranted to explore the efficacy and safety of treatment in those who may benefit from early antiviral treatment. Before such evidence is available, it is still too early to apply antiviral treatment to infants with HBV infection.

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Conflict of interest

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

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Authors' contributions

Conception and writing: HLC, PJC, MHC.

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Supplementary data

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Reply to: Correspondence relating to the manuscript "Early initiation of antiviral therapy contributes to a rapid and significant loss of serum HBsAg in infantile-onset hepatitis B"

To the Editor:

We thank Chen *et al.* and Liu *et al.* for their interest in our article[1] and we also thank the *Journal of Hepatology* for the opportunity to reply to their comments.

First, all mothers of the infants in our study had positive serum HBsAg and HBeAg and a high-level of HBV DNA. These mothers and other family members were always worrying about whether their babies were infected with HBV. Therefore, these infants received relevant tests under their parents' requests, though they did not have apparent clinical symptoms. As professionals in the field of pediatric hepatology in HBV endemic areas, we believe that Dr. Chen and colleagues can profoundly understand the anxieties from these HBsAg-positive mothers.

Second, significant differences in the baseline characteristics existed between the infants in Group I in our study and the infants with non-fulminant hepatitis in the reference paper.[2] For example, among the infants in Group I in our study, HBV genotype C predominated and their mothers were all positive for HBeAg; while in the reference paper, HBV genotype B appeared to be prominent and 11/18 infants were born to HBeAg-negative mothers. According to the results in the reference paper that there was a statistical significance in maternal HBV status between the infants becoming chronic carriers (7/7 with HBeAg-positive mothers) and those recovering from infantile hepatitis B (11/13 with HBeAg-negative mothers), infants in our study seemed to be more likely to develop chronicity. Indeed, no infants in Group II developed spontaneous HBsAg loss before 1 year of age.

Additionally, Chen *et al.* mentioned the 2 HBeAg-negative infants at baseline. Both of them had persistence of HBsAg and a high-level of HBV DNA for more than 6 months.

Third, it is an important question whether infants or younger children with infantile-onset hepatitis B need to be treated. In my opinion, it is worthwhile to report the currently available data and to contemplate their merits. A recent investigation has shown that only 2 in 103 children with chronic hepatitis B (CHB) are eligible for treatment according to the current guidelines, which indicates low therapeutic coverage.[3] In our study, eventually, a total of 17 infants achieved HBsAg seroconversion and 1 developed HBeAg seroconversion in Group I. The seroconversion rate of HBsAg arrived at 94.44% (17/18). In contrast, the spontaneous HBsAg seroconversion rate in the reference paper[2] was 13/20 (65%). Should we choose to treat infantile-onset hepatitis B at an early stage, using safe and effective antivirals to significantly improve the HBsAg seroconversion rate, or choose to leave these infants in long-term follow-up waiting for the uncertain occurrence of spontaneous HBsAg seroconversion, while family members' experience severe anxiety regarding probable worse consequences? I believe every clinician has an answer.

Fourth, regarding the comments from Liu *et al.*, a problem raised by them still puzzles us. In their letter, they cited a paper by Yotsuyanagi *et al.* to indicate that the clearance of HBV in