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

To the Editor:

One article with impressive results was published in a recent issue of this *Journal*. Zhu *et al.* presented us with a study on infantile-onset hepatitis B, which was successfully treated with early antiviral treatment, resulting in the highest HBsAg seroconversion rate we have ever witnessed.[1] We believed that this result is vital for the ulterior management of infantile chronic hepatitis B (CHB), but we have some concerns about this paper.

First of all, we find it hard to distinguish whether these infants with onset hepatitis are in the acute infection period or reactivation stage of chronic infection. We understand that these 2 types of HBV infection have disparate outcomes. Generally, CHB is defined as persistence of HBsAg or being HBV DNA positive for at least 6 months, with a preceding incubation period of 6 weeks to 6 months after infection. In this study, the earliest time at which treatment was started was 6 months of age and we are not sure if all the infants were infected at birth. Besides, Yotsuyanagi *et al.* have previously reported that the clearance of HBV in adulthood can happen between 6 to 12 months from the onset of acute infection.[2] Though a similar scenario was not reported in infancy, we still suggest not to neglect this possibility, and we supposed that some infants in this study were still in the acute infection period when HBsAg clearance occurred.

In addition, infants in group 2, before 1 year of age, are categorized as the no-treatment control with balanced baseline characteristics. However, several confounding factors were not fully justified as the grouping was determined by the parents but not randomization. The standard deviation of alanine aminotransferase (ALT) in group 1 was extremely large (357 ± 303 IU/L). We speculate that many more infants in group 1 presented with ALT over 10 times the upper limit of normal (40 IU/L), which is associated with a high chance of spontaneous clearance. The mean ALT in group 1 was also higher than that in group 2, although the p value did not reach statistical significance due to the limited sample size. The specific HBV DNA and HBsAg titers during screening, prior to treatment initiation, were not described in this article. Any decrease of HBsAg or HBV DNA during this period might also indicate spontaneous clearance and should be balanced between groups.

In brief, the high efficacy of antiviral treatment in group 1 can be partially explained by the possible high percentage of patients in the acute infection period.

The second question is about the outcome of infants who choose not to start antiviral treatment. As the flowchart in this study did not provide a clear procedure for patient screening, selection bias cannot be totally ruled out. We are not sure if there are some patients who fulfilled the inclusion criteria but were not included in the study as their parents did not agree to start antiviral treatment at such a young age.

Collectively, we fully support that this is an important study. However, at this stage, it is too early to adjust the guideline recommendations based on the inspiring results from this study. Further prospective, randomized, controlled studies are urgently needed.

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

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

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.07.022.

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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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