Editorial

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Treatment of infants with hepatitis B virus: A window of opportunity?

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The high global prevalence of chronic hepatitis B infection (3.5%, or 257 million people) is largely sustained by vertical transmission from mother to infant.[1] Most infants who acquire hepatitis from their mothers develop chronic infection and face a lifetime risk of early death from hepatocellular carcinoma or the complications of cirrhosis. Although such severe outcomes may occur during childhood, they are rare in the pediatric age range and are further reduced by access to expert medical care and antiviral therapy when needed.[2–4] However, children with chronic hepatitis B often suffer impaired quality of life and stigmatization, may transmit the virus to others, and may develop liver fibrosis during childhood that eventually results in adverse clinical outcomes during adulthood. Effective prevention and treatment of chronic hepatitis B infection in children are therefore important goals.

Strategies to achieve the elimination of hepatitis B infection rely heavily on newborn immunization. When delivered to a newborn within 24 hours of birth and followed by 2 subsequent doses, the hepatitis B vaccine is approximately 90% effective at preventing perinatal hepatitis B infection. Vaccine failure rates can be further reduced by antiviral treatment of HBV-infected pregnant mothers.[5] Vertical transmission of hepatitis B infection is therefore largely preventable, but newborn immunization programs often struggle to achieve appropriately high levels of coverage for their at-risk populations, and some countries have yet to implement such programs.[6] For now, therefore, large numbers of children continue to acquire new hepatitis B infection every year.

Treatment of hepatitis B infection in these children has mostly been limited to those children with high viral load associated with significant and prolonged elevations of liver enzymes, such that only a small minority of children are treated. Interested in the possibility of widening the eligibility for treatment, several investigators have studied the treatment of children with high viral load, positive hepatitis B e antigen (HBeAg), and normal or near-normal liver enzyme concentrations (*e.g.* alanine aminotransferase [ALT] less than 60 units/liter). This so called "immune tolerant" hepatitis B accounts for the majority of chronically infected children. Five studies have demonstrated conflicting results when evaluating interferon and a nucleoside antiviral agent combination therapy in this phase of infection. In the first study, 23 immune tolerant children, 3–17 years old, were treated with 8 weeks of lamivudine followed by combination therapy with lamivudine and interferon-α for 10 months.[7] Most children (78%) had undetectable HBV DNA levels at end of treatment, 22% seroconverted to anti-HBeAg, and an impressive 17% were negative for antibodies to HBV surface antigen (HBsAg) at end of therapy (far more than expected according to the natural history of the infection). HBV DNA levels rebounded in all individuals that had not seroconverted to anti-HBeAg once therapy was discontinued. The small number of participants limited statistical comparison between responders and non-responders, but there was a suggestion that female, Asian, genotype B, older children were more likely to respond to treatment. Poddar *et al.* subsequently reported 62 "immune tolerant" children (mean age 7 years, ALT <80 U/L), 28 of whom received lamivudine and interferon-α, while 34 who declined therapy formed a control group.[8] In the treatment group, 39% achieved HBeAg seroconversion and 21% became HBsAg undetectable, compared to 6% and 0%, respectively, in the untreated controls. None of the clinical, biochemical or histological variables examined differed between responders and non-responders, although genotype testing was not available.

These encouraging studies from the UK and India contrast with 2 more recent multicenter trials performed by the Hepatitis B Research Network in the United States and Canada.[9,10] Sixty immune tolerant children (age 3–18 years, ALT less than 60 U/L in males and 40 U/L in females) were treated with an initial 8 weeks of entecavir followed by combination of entecavir and peginterferon-α-2a for an additional 40 weeks.[9] All children showed an initial reduction in HBV DNA levels while on treatment, which rebounded in all but 4 children after treatment was stopped. Only 2 children (3%, both Asian, 1 genotype B and 1 genotype C) maintained the primary endpoint of HBV DNA level <1,000 IU/ml and seroconversion to anti-HBeAg at post-treatment week 48, and these 2 patients also showed seroconversion to anti-HBs antibody. Feld *et al.* used a similar regimen in 28 immune tolerant adults and reported that 2% achieved the same primary endpoint 48 weeks after discontinuation of therapy.[10]

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Finally, investigators in Beijing, China studied a different sequence of treatments in children with "immune tolerant" hepatitis B.[11] These investigators reversed the order in which the antiviral therapies were introduced. They randomized 69 children (age 1–16 years, ALT less than 60 U/L, genotype B and C) to an untreated control group or a treatment group who initially received 12-weeks of interferon, followed by 60 weeks of combined interferon and lamivudine therapy, followed by 24 weeks of lamivudine monotherapy, to complete a total 96 weeks of therapy. Outcomes were assessed at treatment week 96. In the treatment group, HBeAg seroconversion was noted in 33% and HBsAg loss in 22%, compared to 4% and 0%, respectively, in the control group. Multivariable analysis revealed higher baseline ALT to be predictive of response to therapy.

Taken together, these 5 studies leave significant questions unanswered as we try to understand the optimal approach to management of children with chronic hepatitis B with high viral load, positive HBeAg and normal or near-normal ALT.[12] We cannot yet be certain of the effects on treatment efficacy of variables such as drug choice (interferon combined with lamivudine *vs.* entecavir), sequence of therapy (interferon monotherapy first, or nucleoside analogue first), viral genotype, or patient characteristics (sex, age, race, ALT, *etc.*). At best, about a third of children with immune tolerant HBV infection may develop a durable response (*i.e.* seroconversion to anti-HBeAg and low HBV DNA) using existing therapies, although this proportion may be far smaller according to the North American studies. Alternative strategies are therefore needed to achieve effective treatment for the majority of children with chronic hepatitis B infection.

The experience with one such alternative strategy is reported in this edition of the *Journal of Hepatology*. Zhu *et al.* compared the outcomes of 18 hepatitis B-infected infants with elevated ALT treated under 1 year of age with lamivudine, to the outcomes of 11 similar infants who waited until more than 1 year of age to receive treatment with interferon (interferon is contraindicated under 1 year of age).[13] For infants treated with lamivudine, interferon could be added if HBsAg remained positive after 1 year of age. Similarly, for older infants treated with interferon, lamivudine was added if HBV DNA declined less than 2 logs after 3 months of interferon therapy. Treatment was continued in both groups for 12 months and for those who had not by then achieved HBsAg seroconversion, treatment was continued until HBsAg or HBeAg seroconversion was achieved.

The 2 groups of infants were diagnosed and followed from the same age. Nine of the 18 lamivudine-treated young infants achieved HBsAg loss by 12 months of age, compared to none of the 11 infants who waited until >1 year of age to start interferon treatment. Remarkably, after 12 months of treatment, 83% of lamivudine-treated infants had lost HBsAg and 83% had developed anti-HBs antibody, compared to 36% and 27%, respectively, in the interferon-treated older infants. During longer term follow-up, all participants except 1 interferon-treated infant achieved HBsAg or HBeAg seroconversion and therefore stopped treatment, and none have shown sero-reversion in the median 102-month off-treatment observation period. This treatment response rate is greatly superior to that described in a recent meta-analysis or prior pediatric studies, which found that HBsAg loss occurred in 7–23% of children depending on the duration of follow-up and seroconversion to anti-HBsAg occurred in 5%.[14]

There are scarce published data describing the natural history of hepatitis B infection during infancy. We know little about changes in ALT during these early months, and it is therefore important to note the significant elevation of ALT in the infants included in the Zhu *et al.* study at baseline (mean values of 357 and 209 U/L in the 2 groups). This suggests that the investigators included only a select group of infants with very active hepatitis, who may respond differently to those with normal or mildly elevated ALT. Furthermore, we do not have good data describing the likelihood of spontaneous loss of HBsAg and seroconversion to anti-HBs positivity without treatment during infancy. During the initial few months of follow-up, before reaching 12 months of age, Zhu *et al.*'s delayed interferon treatment group acts as an untreated control group, and during this time (before 12 months of age), HBsAg seroconversion rates are much higher in the lamivudine-treated group. The published literature provides little additional information on events in this very young age group. In a natural history study of children with chronic hepatitis B infection in Taiwan, 72 vertically-infected infants were included among the total cohort of 415 children, and 7 of these 72 (9.7%) developed HBeAg seroconversion in the first 3 years (median age at seroconversion 1.8 years, range 1.0–2.9 years), but no information was provided about HBsAg seroconversion.[15]

We also understand little about host and hepatitis B virus interactions during infancy. Early suggestions that a "defective" neonatal immune system fails to respond to hepatitis B and thus enables chronic infection have been challenged by evidence that newborn infants mount hepatitis B-specific T-cell responses. The "immune tolerant" phase of hepatitis B (defined by viral markers and ALT level) in older children is characterized by evidence of HBV-specific immune activity, although this activity is weak.[16] In general, the newborn immune system differs from older children and adults in its greater production of anti-inflammatory cytokines, lesser production of pro-inflammatory cytokines, its Th2/TReg predominant T-cell responses and differences in innate immune activity mediated by toll-like receptors.[17,18] We must await further studies to determine how this may impact responses to antiviral therapies.

Because the clinical benefit of combination antiviral therapy for children with "immune tolerant" hepatitis B is uncertain and unimpressive, there is a pressing need to identify more widely effective ways to treat children with hepatitis B. The small study by Zhu and colleagues provides hope that novel timing of treatment during infancy may facilitate a far greater likelihood of successful antiviral therapy, including HBsAg seroconversion. Treatment of young infants cannot yet be clinically recommended based on these data, but a potential window of opportunity in early life has been identified for further study, when the relationship between host and hepatitis B virus may be more susceptible to disruption by current antiviral agents.

Conflict of interest

Dr. Ling reports grants from Abbvie, grants from Gilead, grants from Bristol Myers Squibb, outside the submitted work. Dr Mogul has nothing to disclose.

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

Supplementary data

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