The Efficacy of Tenofivir to Prevent Perinatal Transmission in Chronic Hepatitis B Mothers. A Clinical Perspective

TO THE EDITOR:

With great satisfaction, we read the April 2018 American Association for the Study of Liver Diseases (AASLD) guidelines for the management of chronic hepatitis B propose that pregnant women with hepatitis B virus (HBV) receive tenofovir in the third trimester, for viral loads greater than 200,000 IU/mL.[1]

Surprisingly, the first double-blinded, randomized, controlled trial on this subject, released in the March 8 issue of the *New England Journal of Medicine*, found no significant difference between fetal viral loads of a group of 147 women who received tenofovir beginning at 28 weeks and those of a control group who did not. The researchers concluded that there was no benefit to prescribing tenofovir in the third trimester of pregnancy.[2]

These results contrast with the thinking that the AASLD has carefully substantiated and cultivated in the hepatology community in recent years. The conclusion reached by the researchers of this study is counterintuitive, because 3 patients in their placebo group developed hepatitis B, whereas none in the treated group became infected. It is noteworthy that the mothers of all 3 infected infants in the treated group had HBV-DNA levels of more than 7.8 log10 IU/mL. Such high viral loads may well be refractory to antiviral rescue during pregnancy. However, there are certainly a substantial number of mothers with viral loads somewhere between 200,000 and 1 million who can benefit from tenofovir. This particular trial simply cannot define the most precise group of potential beneficiaries.

A randomized, open-label trial published in 2016 studied 200 mothers with viral loads greater than 200,000 IU/mL and concluded that the rate of mother-to-child transmission was lower among those who received tenofovir disoproxil fumarate therapy than among those who received care without antiviral therapy. The researchers endorsed the use of tenofovir as outlined in the recent AASLD guidelines. We are not told viral loads of the mothers of tenofovir failures in this 2016 study, but it is possible that these mothers had initial viral loads that were several orders of magnitude greater than other viremic mothers who may have responded.[3]

It is therefore not reasonable to conclude from the March 2018 controlled trial that tenofovir is of no benefit to mothers with viral loads greater than 200,000 IU/mL. There may be, however, a higher threshold beyond which tenofovir will no longer do the job. For the time being, the new AASLD guidelines must be followed. Perhaps, in the future, there will be a more potent antiviral agent that can eradicate much higher viral loads during pregnancy.

Ghassan Mubarak, M.D.
Richard Ferstenberg, M.D.
Department of Internal Medicine, State University of New York Downstate Medical Center, Brooklyn NY

REFERENCES

1) Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67:1560-1599.
2) Jourdain G, Ngo-Giang-Huong N, Harrison L, Decker L, Khamduang W, Tierney C, et al. Tenofovir versus placebo to prevent perinatal transmission of hepatitis B. N Engl J Med 2018;378:911-923.
3) Pan CQ, Duan Z, Dai E, Zhang S, Han G, Wang Y, et al.; China Study Group for the Mother-to-Child Transmission of Hepatitis B. Tenofovir to prevent hepatitis B transmission in mothers with high viral load. N Engl J Med 2016;374:2324-2334.

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep.30138

Potential conflict of interest: Nothing to report.

REPLY:

Prevention of mother-to-child transmission of hepatitis B virus (HBV) is a major component of the HBV elimination efforts in every country. We thank Drs. Mubarak and Ferstenberg for highlighting the American Association for the Study of Liver Diseases (AASLD) 2018 updated hepatitis B guidance on prevention of mother-to-child transmission[1]

and conclusions from a recently published randomized clinical trial by Jourdain et al. of tenofovir disoproxil fumarate (TDF) versus placebo in pregnancy.[2] In the Jourdain et al. study, TDF was not associated with a statistically significant reduction in perinatal transmission of HBV, but the 2% rate of perinatal transmission with placebo was much lower than the expected 12%, leaving the study underpowered to detect a statistically significant difference. Notably, no infants became infected in the TDF-treated group, similar to another randomized trial comparing third-trimester TDF to placebo.[3]

The cornerstone of prophylaxis of infants born to HBV surface antigen–positive women is timely administration of passive immunization with hepatitis B immune globulin (HBIG) and HBV vaccine. HBIG and the first dose of the vaccine should be given as soon as possible after birth and no later than 12 hours postdelivery.[1] Most strikingly, the Jourdain et al. study achieved a very short interval between birth and administration of HBIG (median 1.3 hours) and HBV vaccine (median 1.2 hours),[2] thereby demonstrating the effectiveness of ideally delivered immunoprophylaxis. Despite this, transmission still occurred only in the placebo (and not the TDF-treated) group. Additionally, their results may not reflect "real-world" settings, where timing of HBIG and vaccine is likely to be more variable. Indeed, only 71.1% of newborns in the United States in 2016 received the first dose of HBV vaccine within 3 days of birth.[4] Thus, the AASLD continues to advocate for use of antiviral therapy in the third trimester for women with high HBV DNA levels as an additional measure to reduce perinatal transmission of HBV.

Mubarak and Ferstenberg suggested that women with very high HBV DNA levels may be at risk for failure of antiviral prophylaxis. In our prior systematic review, an HBV DNA level of 200,000 IU/mL was the threshold below which perinatal transmission was not seen. The AASLD guidance recommends antiviral therapy if baseline HBV DNA is >200,000 IU/mL, a threshold selected to reduce the rate of perinatal transmission to as close to zero as possible. In clinical trials of immune active hepatitis B e antigen–positive persons, median decline in HBV DNA was –3, –3.78, –4.36, and –4.92 $\log_{10}$ after 4, 8, 12, and 16 weeks of TDF.[5] Thus, for women with very high levels of HBV DNA (>10^9 IU/mL) during pregnancy, starting treatment earlier than weeks 28-32 may be prudent to achieve HBV DNA ≤200,000 IU/mL at the time of delivery. The current AASLD guidance recommendation to start TDF at weeks 28-32 of gestation is reasonable; however, a more individualized approach based on maternal viral load earlier in pregnancy and anticipated time of delivery could be considered to achieve sufficient suppression of HBV DNA to prevent HBV transmission.

Norah A. Terrault, M.D., M.P.H.[1]
Robert S. Brown, Jr., M.D., M.P.H.[2]
Anna S.F. Lok, M.D.[3]
John B. Wong, M.D.[4]
Natalie H. Bzowej, M.D., Ph.D., F.R.C.P.C.[5]
Kyong-Mi Chang, M.D.[6]
Jessica P. Hwang, M.D., M.P.H.[7]
Maureen M. Jonas, M.D.[8]
Brian J. McMahon, M.D., M.A.C.P.[9]
[1]Division of Gastroenterology/ Hepatology, University of California San Francisco, San Francisco, CA
[2]Division of Gastroenterology and Hepatology, Weill Cornell Medical College New York, NY
[3]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, MI
[4]Division of Clinical Decision Making, Tufts Medical Center, Tufts University School of Medicine, Boston, MA
[5]Ochsner Medical Center, New Orleans, LA
[6]Division of Gastroenterology, Corporal Michael J. Crescenz VA Medical Center, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA
[7]Department of General Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX
[8]Division of Gastroenterology, Hepatology and Nutrition, Boston Children's Hospital Boston, MA
[9]Liver Diseases and Hepatitis Program Alaska NativeTribal Health Consortium Anchorage, AK

REFERENCES

1) Terrault NA, Lok AS, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment and of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67:1560-1599.
2) Jourdain G, Ngo-Giang-Huong N, Harrison L, Decker L, Khamduang W, Tierney C, et al. Tenofovir versus placebo to prevent perinatal transmission of hepatitis B. N Engl J Med 2018;378: 911-923.

3) Pan CQ, Duan Z, Dai E, Zhang S, Han G, Wang Y, et al. Tenofovir to prevent hepatitis B transmission in mothers with high viral load. N Engl J Med 2016;374:2324-2334.
4) Hill HA, Elam-Evans LD, Yankey D, Singleton JA, Kang Y. Vaccination coverage among children aged 19–35 months—United States, 2016. MMWR Morb Mortal Wkly Rep 2017;66:1171-1177.
5) **Chan HL, Fung S**, Seto WK, Chuang WL, Chen CY, Kim HJ, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol 2016;1:185-195.

Author names in bold designate shared co-first authorship.

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep.30137

Potential conflict of interest: Dr. Terrault received grants from Gilead and Bristol-Myers Squibb. Dr. Brown consults for and received grants from Gilead. He consults for Bristol-Myers Squibb. Dr. Jonas consults for and received grants from Gilead. She received grants from Bristol-Myers Squibb, Roche, AbbVie, and Merck. Dr. Bzowej received grants from Gilead, Allergan, and Cirius. Dr. Lok received grants from Gilead and Bristol-Myers Squibb.

Allogeneic Mesenchymal Stem Cells Therapy for the Treatment of Hepatitis B Virus–Related Acute-on-Chronic Liver Failure

TO THE EDITOR:

We read with great interest the recent publication by Lin et al.[1] Recently, mesenchymal stem cells (MSC) have been considered a novel and effective therapy for liver diseases such as liver fibrosis, cirrhosis, and liver failure. In this paper, the authors demonstrated the significant survival benefit of allogeneic bone marrow MSC (BMSC) for hepatitis B virus–related acute-on-chronic liver failure (ACLF) in comparison with standard medical treatment. However, optimization of this therapeutic strategy is more valuable for MSC treatment. There are several aspects that should be taken into consideration. First, the number of infused MSC is the primary consideration. In this study, patients in the BMSC group received different infusion doses ranging from 1.0 to 10×10^5 cells/kg. Several previous studies revealed that a larger number of infused MSC was associated with more satisfied efficacy. Nakamura et al.[2] study showed that transplantation of human $CD34^+$ cells after chronic liver injury aroused the regeneration of liver function in a dose-dependent manner. Therefore, in BMSC efficacy assessment, it is necessary to conduct subgroup analysis based on the different cell dosages. Second, studies showed that infusion of MSC through hepatic artery improved liver function more effectively than intravenous perfusion.[3] This may be because transplantation through hepatic artery can deliver a larger number of transplanted cells to the damaged liver parts, thereby stimulating hepatic regeneration more efficiently. Therefore, investigation of the different effects of BMSC for ACLF using different routes of cell administration will benefit its clinical application. Lastly, allogeneic BMSC were used for the treatment ACLF in this study. Human umbilical cord is another source of MSC that demonstrates advantages over BMSC with a wider range of collection sources, easier noninvasive approach, and fewer ethical constraints.[4] Therefore, using umbilical cord instead of bone marrow as the cell source may be more feasible for the treatment of ACLF. On the other hand, the number of cells extracted from an umbilical cord specimen is far more than that of a bone marrow specimen, which can eliminate the individual differences of MSC therapeutic effects. In summary, it would be more meaningful if the authors can investigate these aspects in the curative effects of BMSC therapy.

Changhui Zhou, M.S.[1]
Weihua Wang, M.S.[1]
Ying Mu, M.D.[2]
[1]**Department of Central Laboratory**
Institute for stem cell clinical research
Liaocheng People's Hospital
Liaocheng Clinical School of Taishan Medical University
Liaocheng, Shandong Province, China
[2]**Department of Gastroenterology**
Liaocheng People's Hospital
Liaocheng Clinical School of Taishan Medical University
Liaocheng, Shandong Province, China