

## ABSTRACT

# 1 | TENOFOVIR-DF THERAPY PREVENTS HEPATITIS B VERTICAL TRANSMISSION IN HIGHLY VIREMIC MOTHERS WITHOUT HBV IMMUNOGLOBULIN FOR INFANTS

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**Background:** Maternal tenofovir disoproxil fumarate (TDF) in combination with an infant's passive-active immunoprophylaxis is recommended by WHO for mothers with HBV-DNA >200,000 IU/mL. Because of the shortage of immunoglobulin (HBIG) in many developing countries, we aimed to study maternal TDF therapy initiated in the second trimester with an infant's HBV vaccination and omission of HBIG for preventing mother-to-child transmission (MTCT). **Methods:** In a multicenter RCT from 6/4/2018 to 2/8/2022, we randomly assigned CHB mothers with HBV-DNA >200,000 IU/mL (ratio, 1:1) to receive TDF from gestational weeks 14-16 (experimental group) or week 28 (control) to delivery. All infants received active immunoprophylaxis and HBIG was only given to infants in the control group. The primary outcomes were the congenital defects/malformation rates and MTCT rates (i.e., HBsAg+ or HBV-DNA >20 IU/mL) at the infant's age of 28 weeks. Secondary assessments were safety analyses (ClinicalTrials.gov: NCT03476083). **Results:** Of the 280 HBeAg+ mothers enrolled, 265 mothers and 269 infants completed the study (95% retention). The participants' characteristics are shown in Table 1. At delivery, a significantly lower median (IQR) HBV-DNA level ( $\log_{10}$  IU/mL) was noted in the experimental group (2.37 [1.88, 3.08] vs 3.62 [2.86, 4.59];  $p < 0.001$ ), with a similar trend in the percentage of mothers with HBV-DNA <200,000 IU/mL (99.2% vs 94.2%;  $p = 0.04$ ). The congenital defect rates did not differ significantly between groups (3.1% [4/131] vs 6.4% [9/141];  $p = 0.22$ ). At the postpartum week 28, 128/128 and 137/141 mother/infant dyads in the experiment and the control groups were analyzed, respectively. The per-protocol analysis revealed 0% of MTCT in both groups. The maternal HBeAg/HBsAg (-) rates did not differ significantly between groups. TDF was well-tolerated without discontinuation from severe adverse events (SAEs). Safety parameters were comparable both in frequency and severity between the two groups including estimated glomerular filtration rates during treatment, postpartum ALT flares, and SAEs. **Conclusion:** In highly viremic CHB mothers, we observed that TDF initiated at gestational weeks 14-16 reduced MTCT to 0% when infants received HBV vaccines without HBIG, which also had similar safety outcomes when compared to those of mothers who initiated TDF at gestational week 28. Our data support

the signaling of collagen catabolic process, extracellular matrix structural constituent and negative-regulation of JAK-STAT cascade etc. **Conclusion:** Improvement of liver fibrosis post DAA treatment could be affected by the change of miRNAs expression profile in the liver and serum.

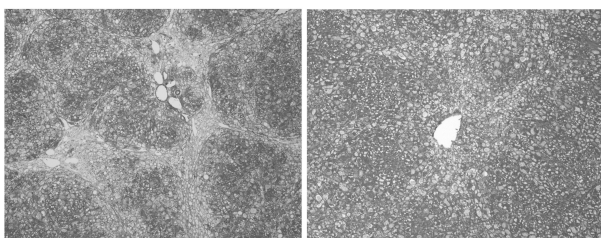
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### 1426 | HUMAN PLACENTAL EXTRACT ATTENUATES HEPATIC FIBROSIS AND CIRRHOSIS IN RATS WITH NONALCOHOLIC STEATOHEPATITIS

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**Background:** Nonalcoholic steatohepatitis (NASH) is always accompanied with hepatic fibrosis that could potentially progress to liver cirrhosis and hepatocellular carcinoma (HCC). Employing a rat model, we evaluated the role of human placental extract (HPE) to arrest the progression of hepatic fibrosis to cirrhosis and HCC in patients with NASH. **Methods:** SHRSP5/Dmcr rats were fed with a high-fat and cholesterol diet for 4 weeks and evaluated the development of steatosis. The animals were divided into control and treated groups and received either saline or HPE (3.6 mg/kg body weight) subcutaneously thrice a week. A set of control and HPE treated animals were sacrificed at



Azan staining for collagen in the liver sections of SHRSP5/Dmcr rats fed with a high-fat and cholesterol diet for 12 weeks and after the treatment with human placental extract (HPE) at a dose of 3.6 mg/kg body weight for 8 weeks. Azan staining demonstrated well developed fibrosis and early cirrhosis in untreated control animals at 12 weeks. Treatment with HPE for 8 weeks prevented formation fibrous septa, depicted marked reduction in the deposition of collagen fibers, and significant decrease of hepatic fibrosis.

the end of 6th, 8th, and 12th weeks from the beginning of the experiment. Blood and liver samples were collected for biochemical studies and histopathological evaluations. Immunohistochemical staining was performed for  $\alpha$ -SMA, TNF- $\alpha$ , 4-hydroxy-2-nonenal (4-HNE), collagen type I, and type III. **Results:** Control rats depicted progression of liver fibrosis at 6 weeks, advanced fibrosis and bridging at 8 weeks, and cirrhosis at 12 weeks, which were significantly decreased in HPE treated animals. Immunohistochemical staining demonstrated marked decrease in the staining intensity of  $\alpha$ -SMA, TNF- $\alpha$ , 4-HNE, and both collagen type I and type III in HPE treated rats compared to control animals. **Conclusion:** The results of the present study indicated that HPE treatment mediates immunotropic, anti-inflammatory, and antioxidant responses and attenuates hepatic fibrosis and cirrhosis. Therefore, HPE may be used as a therapeutic agent to prevent progression of liver fibrosis to cirrhosis in patients with NASH. \*Presenting author Email: georgej@kanazawa-med.ac.jp

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### 1427 | ACTIVATION OF LXR/RXR REVERSES HEPATIC FIBROSIS IN ATP7B-/- (WILSON DISEASE) MICE VIA NON-CANONICAL TGF $\beta$ SIGNALING PATHWAY

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**Background:** Wilson disease (WD) is caused by inactivation of the copper-transporter ATP7B, associated elevation of hepatic copper (Cu) and reduction in nuclear receptor (NR) function. Activation of the liver X receptor/retinoid X receptor (LXR/RXR) pathway in *Atp7b*<sup>-/-</sup> mice prior to the development of hepatitis improves liver function and delays the development of fibrosis without Cu chelation. Here, we tested whether activation of LXR/RXR after the onset of disease will reverse fibrosis and characterized the associated signaling mechanisms. **Methods:** *Atp7b*<sup>-/-</sup> (knockout) and *Atp7b*<sup>+/-</sup> (heterozygous) mice of C57BL/6x129S6/SvEv background were fed with a LXR agonist, T0901317 for 8 weeks starting at 12 weeks (advanced disease stage) after birth. Total RNA-sequencing in male livers was performed to identify the affected metabolic and signaling pathways. Indicators of fibrosis were evaluated by qRT-PCR, Western blotting (WB), immunofluorescence