

Abstracts

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Post-Graduate Program (Hepatitis B)

PG1-1

Chronic Hepatitis B Virus Infection

Dr. Wan-Long Chuang

Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University Taiwan

Chronic hepatitis B virus (HBV) infection is a serious global health issue. Chronic HBV infection might lead to liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC). Thus, the goal of treatment for chronic hepatitis B (CHB) is to improve survival and quality of life by preventing transmission, disease progression and HCC. Chronic HBV infection comprises four phases defined as immune tolerant phase, immune clearance phase (HBeAg-positive chronic hepatitis), inactive carrier phase, and reactivation phase (HBeAg-negative chronic hepatitis). Treating the patients with immune active chronic hepatitis B (both HBeAg-positive and negative) is recommended to decrease the risk of liver-related complications. Pegylated interferon and nucleos(t)ide analogues (NAs, including entecavir, tenofovir disoproxil fumarate and tenofovir alafenamide) are the preferred first line agents for CHB treatment. NAs are selected because of convenience, good tolerability, safety, high potency and minimal to no risk of resistance. However, NAs have no direct action on cccDNA, and long-term NAs therapy is required to maintain HBV suppression in HBeAg negative patients. There are several concerns, e.g. financial burden, adherence and willingness, for indefinite long-term NAs therapy. In addition, increase rates of HBsAg loss are observed after cessation of NAs treatment in HBeAg-negative patients. Finite NAs therapy in selected HBeAg-negative CHB becomes a recommendation. Discontinuation of NAs treatment in patients with cirrhosis is not recommended. For HBeAg-positive adults without cirrhosis who seroconvert to anti-HBe on NAs therapy, discontinue therapy after a period of consolidation treatment is suggested. NAs may be discontinued in HBeAg-negative patients without cirrhosis, who achieve long-term virological suppression. Decompensation and severe ALT flare may occur after cessation of NAs, especially in patients with liver cirrhosis. Close monitoring is warranted for the HBeAg-negative patients stopping NAs treatment. If hepatic decompensation developed, re-starting NA therapy should be given immediately. For patients with virological or

clinical relapse, treatment indications for naïve CHB patients may be applied.

Post-Graduate Program (Hepatitis B)

PG1-2

Epidemiology, Genotype Distribution, Prognosis and Treatment of Viral Hepatitis C and HCC in Mongolia

Dr. Oidov Baatarkhuu

Department of Infectious Diseases, Mongolian National University of Medical Sciences Mongolia.

In Mongolia, morbidity from liver cancer is 68.1 per 100 000 population, which is eight times higher than the global average. This is directly associated to the higher rate of morbidity of chronic hepatitis caused by HBV, HCV and HDV. Prevalence of HCV in Mongolia was high. The predominant genotype of HCV among general populations in Mongolia is 1b.

Between 2015 to 2019, 23 (0.5%) and 5,005 patients (99.5%) with genotype 1a and 1b HCV, respectively, were treated with a fixed-dose tablet containing 90 mg ledipasvir and 400 mg sofosbuvir for 12 weeks, and 81 patients (1.6%) with previous experience of interferon (IFN)-based treatment received additional 1,000 mg ribavirin. Most patients (n = 5,008; 99.6%) achieved ETR and SVR12 without virologic relapse. Patients with genotype 1a showed low rates of ETR and SVR12 in only 16 patients (69.6%). There was no significant difference in SVR12 rate between patients regardless of IFN experience (n = 81; 1.6%), cirrhosis (n = 1,151; 22.9%), HCV RNA > 6 × 10⁶ IU/mL (n = 866; 17.2%), or liver stiffness > 9.6 kPa (n = 1,721; 34.2%) (100.0%, 99.3%, 99.4%, and 99.4%, respectively). The most common AEs were headache (n = 472; 9.4%), fatigue (n = 306; 6.2%), abdominal discomfort (n = 295; 5.9%), and skin rash (n = 141; 2.8%).

Most patients had advanced HCC – 88 (45.1%) in stage III and 57 (29.2%) in stage IV. The risk factors associated with HCC development were history of acute hepatitis, chronic hepatitis, and the presence of liver cirrhosis. The most common etiology for HCC in our patients was HCV infection which is 46%, HBV infection -34%, coinfection B and C -14% and others which is 6.0%. According to the results of our study over 65% of patients had tumor size more than 5

lowering effect was associated with higher LDL-receptor (+39%) and lower apolipoprotein B (-17%) hepatic gene expression (both $p < 0.01$). Resmetirom reduced hepatic triglycerides content (-25%, $p < 0.01$) and significantly reduced NAFLD activity score through lower inflammation score ($p < 0.01$), as well as lower IL-6 and IL-1 β hepatic gene expression (both $p < 0.05$). Resmetirom also showed anti-fibrotic effects as shown by a significantly lower % Sirius Red labelling.

Conclusion: Resmetirom lowers LDL-cholesterol, hepatic inflammation, and fibrosis in the 3-week MASH mouse model. This preclinical model will be useful to expedite preclinical drug development for the treatment of MASH.

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P-0272

Treatment with human placental extract ameliorates metabolic-associated fatty liver disease

Joseph George¹, Mikihiro Tsutsumi¹, Mutsumi Tsuchishima¹

¹Department of Hepatology, Kanazawa Medical University Uchinada, Ishikawa Japan

Background: Metabolic-associated fatty liver disease (MAFLD) is characterized by the intense deposition of fat globules in the hepatic parenchyma. Uncontrolled MAFLD may develop into fibrosis, which could potentially progress to liver cirrhosis and hepatocellular carcinoma. We evaluated the effect of human placental extract (HPE) to prevent the progression of MAFLD to hepatic fibrosis and cirrhosis.

Methods: SHRSP5/Dmcr rats (spontaneously hypertensive rats/stroke prone) were fed a high-fat and cholesterol (HFC) diet for 4 weeks and screened for steatosis. A set of animals on HFC diet were treated with HPE (3.6 mg/kg body weight) subcutaneously thrice a week, and another set served as control. The animals were sacrificed at 12 weeks from the beginning of the experiment.

Results: The animals fed with HFC diet depicted well-developed fibrosis with bridging and early cirrhosis. Immunohistochemical staining for α -SMA and 4-hydroxy-2-nonenal (4-HNE) demonstrated activation of hepatic stellate cells and marked increase in lipid peroxidation, respectively. Staining for collagens type I and type III depicted marked deposition of newly formed collagen fibers in the hepatic parenchyma. Animals treated with HPE demonstrated significant reduction in biochemical and histopathological changes compared to the respective control group.

Conclusion: The results of the present study indicated that treatment with HPE could ameliorate MAFLD and might be suitable to use as a therapeutic agent to prevent the progression of steatosis to hepatic fibrosis and cirrhosis. Various cytokines, growth factors, anti-inflammatory agents, and antioxidant molecules present in HPE might contribute towards the amelioration of MAFLD.

Email: georgej@kanazawa-med.ac.jp

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P-0273

Macrophages release miRNA-enriched extracellular vesicles that are taken up by lipotoxic hepatocytes

Bootsakorn Boonkaew¹, Kenneth W. Witwer², Pisit Tangkijvanich¹

¹Center of Excellence in Hepatitis and Liver Cancer, Department of Biochemistry, Faculty of Medicine, Chulalongkorn University Bangkok Thailand, ²Department of Molecular and Comparative Pathobiology, Johns Hopkins University School of Medicine Baltimore Maryland

Introduction: Lipotoxicity and inflammation in the liver play a critical role in the development of nonalcoholic fatty liver disease (NAFLD). Extracellular vesicles (EVs) carry microRNAs (miRs) to modulate cellular crosstalk. Here, we investigated whether miR-223 can be transported from macrophages to lipotoxic hepatocytes via EVs.

Methods: To demonstrate that macrophages transfer EVs containing miR-223 to hepatocytes, we transfected macrophages with a Cy3-miR-223 mimic. Co-culture between the transfected macrophages and the palmitic acid induced-lipotoxic hepatocytes was performed on a transwell system for 24 hours, and miR-223 and its target genes in the hepatocytes was examined. EV uptake assay was also measured by labelling macrophage-derived EVs with MemGlow 488, and incubating them with lipotoxic hepatocytes. Low-density lipoprotein receptor (LDLR) in the lipotoxic hepatocytes was measured.

Results: We found that miR-223 was highly expressed in EV fractions from the transfected macrophages. Upon co-culture, the lipotoxic hepatocytes displayed Cy3 fluorescence and exhibited an increase in miR-223 levels and a decrease in miR-223 target genes, *FOXO3* and *TAZ*, as compared to the control group. Blocking EV secretion from macrophages with GW4869 led to reduced transfer of miR-223 to hepatocyte recipient cells. The MemGlow dye was transferred to lipotoxic hepatocytes when incubated with MemGlow-labeled EVs from macrophages. The results also suggested that LDLR played a partial role in facilitating EV uptake by lipotoxic hepatocytes.

Conclusions: Our results show that macrophages transfer miR-223 to lipotoxic hepatocytes predominantly by EV-dependent manner.

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P-0274

A Systematic Review for Adjusting High-fat/High-fructose Animal Models to Clinical Feature of NAFLD

Yu-Jin Choi¹, Chang-gue Son²

¹Se-Myung University Jecheon-si South Korea, ²Daejeon University Daejeon South Korea

Background: The complexities of the etiology and pathophysiology of Non-alcoholic fatty liver disease (NAFLD) lead to difficulty in development of therapeutics. We aim to assess statistically the diet-related factors contributing to NAFLD progression using animal studies, which would inform both physicians and researchers for the management of patients and for their preclinical studies.

Methods: From both PubMed and Cochrane database, we searched NAFLD data through October 2022, focusing on high-fat, high-fructose diet (HFHFD) rodent model. We extracted the details for the compositions of diet and routes of intake, period of induction, and characteristics of rodents. And then, we conducted correlation analysis and multiple linear regression analysis among those variants.

Results: A total 161 data (116 articles) was final selected, which produced 14 independent variables. Unexpectedly, no variant significantly correlated with the progression of Non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH), while three factors were the key contributing factors in fibrosis progression under multiple regression analysis ($r = 0.717$, $p < 0.001$); as a relative portion by 40.2% of inducing period, 33.2% of fructose-derived