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Liver Digest

A weekly update of PLRC happenings

April 4, 2019

PITTSBURGH LIVER RESEARCH CENTER
A partnership of University of Pittsburgh & UPMC

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Featured Faculty - Dr. Lawrence Vernetti

In this issue

Seminar - Friday, April 5

Starzl Transplant Institute Conference Series Internal Grand Rounds

Vikrant Rachakonda, MD
Assistant Professor of Medicine
Division of Gastroenterology, Hepatology and Nutrition

"Liver Transplantation for Acute Alcoholic Hepatitis"

Friday, April 5, 2019

8:00 a.m. – 9:00 a.m.

LHAS Auditorium - 7 Main - MUH

Sponsored by:
Thomas E. Starzl Transplantation Institute
University of Pittsburgh School of Medicine
Department of Surgery, Division of Transplantation
and
Center for Continuing Education in the Health Sciences

Target Audience: Transplant fellows and faculty (basic and clinical); physician assistants; research associates and assistants; clinical and research nurse coordinators. **Overall Goals of the Program:** To provide cutting-edge information about clinical treatment and research in the transplantation field and related disciplines. **Continuing Education Credit:** This activity is sponsored by the University of Pittsburgh School of Medicine, Center for Continuing Education in the Health Sciences, and the Department of Surgery. The University of Pittsburgh School of Medicine, as part of the Consortium for Academic Continuing Medical Education, is accredited by the Accreditation Council for

Continuing Medical Education to sponsor continuing medical education for physicians. The Center for Continuing Education in the Health Sciences designates this educational activity for a maximum of 1 hour in Category 1 credit toward the AMA Physician's Recognition Award. Each physician should only claim those hours of credit that he/she actually spent in the educational activity. Other healthcare professionals are awarded 0.1 continuing education units (CEUs) which are equal to 1.0 contact hours. Category 1 Continuing Education Points for Transplant Certification (CEPTCs) have been applied for through the American Board for Transplant Certification (ABTC).

For a complete list of upcoming PLRC seminars, please visit our website: **http://www.livercenter.pitt.edu/events**

Liver-Themed Gut Club - May 2

Dr. Fasiha Kanwal, the division chief at Baylor, will speak at the May 2, 2019 Pittsburgh Gut Club accredited dinner/lecture series on "The Changing Epidemiology of Liver Cancer."

Liver-related clinical and research trainees are invited to attend the lecture with fee-waived registration. All faculty are invited to attend as well but are required to pay to attend. But, they welcome your trainees as fee-waived participants.

To register for this event, please complete the registration form found in the brochure available on the here (trainees mark "fee waived" in the payment section), and scan (**joj2@pitt.edu**) or fax (412-578-9537) it to Joy Merusi by April 15th.

Faculty Highlights

Original Article:

Qiao Y, Wang J, Karagoz E, Liang B, Song X, Shang R, Evert K, Xu M, Che L, Evert M, Calvisi DF, Tao J, Wang B, **Monga SP**, Chen X. Axin1 deletion induced hepatocarcinogenesis requires intact β-Catenin but not Notch cascade in mice. Hepatology. 2019 Feb 8. doi: 10.1002/hep.30556. [Epub ahead of print] PubMed PMID: 30737831.

ABSTRACT

Inactivating mutations of AXIN1, a negative regulator of the Wnt/β-Catenin cascade, are among the common genetic events in human hepatocellular carcinoma (HCC), affecting around 10% of cases. In the present manuscript, we sought to define the genetic crosstalk between Axin1 mutants and Wnt/β-catenin as well as Notch signaling cascades along hepatocarcinogenesis. We discovered that c-MET activation and AXIN1 mutations occur concomitantly in ~3 to 5% of human HCC samples. Subsequently, we generated a murine HCC model via CRISPR/Cas9 based gene deletion of Axin1 (sgAxin1) in combination with transposon-based expression of c-Met in the mouse liver (c-Met/sgAxin1). Global gene expression analysis of mouse normal liver, HCCs induced by c-Met/sgAxin1 as well as HCCs induced by c-Met/ΔN90-β-Catenin revealed activation of the Wnt/β-Catenin and Notch signaling in c-Met/sgAxin1 HCCs. However, only a few of the canonical Wnt/β-Catenin target genes were induced in c-Met/sgAxin1 HCC when compared to corresponding lesions from c-Met/ΔN90-β-Catenin mice. To study whether endogenous β-Catenin is required for c-Met/sgAxin1 driven HCC development, we expressed c-Met/sgAxin1 in liver-specific Ctnnb1 null mice, which completely prevented HCC development. Consistently, in AXIN1 mutant or null human HCC cell lines, silencing of β-Catenin strongly inhibited cell proliferation. In striking contrast, blocking the Notch cascade via expression of either the dominant negative form of RBP-

J or the ablation of Notch2, did not significantly affect c-Met/sgAxin1-driven hepatocarcinogenesis. Conclusion: We demonstrated here that loss of Axin1 cooperates with c-Met to induce HCC in mice, in a β-Catenin signaling dependent but Notch cascade independent way.

For full text, please **click here.**

Original Article with Accompanying Editorial:
Adeel A. Butt, Peng Yan, Ashfaq Shuaib, Abdul-Badi Abou-Samra, **Obaid S. Shaikh**, Matthew S. Freiberg. Direct-Acting Antiviral Therapy for HCV Infection Is Associated With a Reduced Risk of Cardiovascular Disease Events. Gastroenterology Volume 156, Issue 4, March 2019, Pages 987-996.e8.

ABSTRACT
Background & Aims: Infection with hepatitis virus C (HCV) is associated with an increased risk of cardiovascular disease (CVD) events. It is not clear whether treatment with direct-acting antiviral (DAA) agents affects risk of CVD.

Methods: We searched the Electronically Retrieved Cohort of HCV-Infected Veterans database for patients with chronic HCV infection (n = 242,680) and identified patients who had been treated with a pegylated interferon and ribavirin regimen (n = 4436) or a DAA-containing regimen (n = 12,667). Treated patients were matched for age, race, sex, and baseline values with patients who had never received treatment for HCV infection (controls). All subjects were free of any CVD event diagnosis of HCV infection at baseline. The primary outcome was incident CVD events, identified by International Classification of Diseases, Ninth Edition, Clinical Modification or International Classification of Diseases, Tenth

Edition code, in the different groups and in patients with vs without a sustained virologic response to therapy.

Results: There were 1239 (7.2%) incident CVD events in the treated groups and 2361 (13.8%) events in the control group. Incidence rates were 30.9 per 1000 patient-years (95% CI 29.6–32.1) in the control group and 20.3 per 1000 patient-years (95% CI 19.2–21.5) in the treated groups (P < .0001). Treatment with pegylated interferon and ribavirin (hazard ratio 0.78; 95% CI 0.71–0.85) or a DAA regimen (hazard ratio 0.57; 95% CI 0.51–0.65) was associated with a significantly lower risk of a CVD event compared with no treatment (controls). Incidence rates for CVD events were 23.5 per 1000 patient-years (95% CI 21.8–25.3) in the group treated with the pegylated interferon and ribavirin regimen, 16.3 per 1000 patient-years (95% CI 14.7–18.0) in the group treated with a DAA regimen, and 30.4 (95% CI 29.2–31.7) in the control group. A sustained virologic response was associated with a lower risk of incident CVD events (hazard ratio 0.87; 95% CI 0.77–0.98).

Conclusions: In an analysis of a cohort of HCV-infected veterans, treatment of HCV infection was associated with a significant decrease in risk of CVD events. Patients treated with a DAA regimen and patients who achieved sustained virologic responses had the lowest risk for CVD events.

For full text, please **click here**.
For accompanying editorial, please **click here**.

Original Article:
Ren T, Yang M, Xiao M, Zhu J, **Xie W**, Zuo Z. Time-dependent inhibition of carbamazepine metabolism by piperine in anti-epileptic treatment. Life Sci. 2019 Feb 1;218:314-323. doi: 10.1016/j.lfs.2018.12.060. Epub 2019 Jan 3. PubMed PMID: 30611786.

ABSTRACT

AIMS: The first-line anti-epileptic agent carbamazepine has narrow therapeutic index and can potentially interact with piperine, the major component from black pepper. The present study aimed to delineate the mechanism of such interaction for safe usage of carbamazepine during epilepsy control.

MATERIALS AND METHODS: The effect of piperine on carbamazepine hepatic metabolism was examined using rat or human liver microsomes. Mechanistic static model was applied to predict the extent of interaction. In addition, liver microsomal activities, mRNAs and protein expressions of genes regulating carbamazepine metabolism were evaluated after two weeks oral administrations of 3.5 and 35 mg/kg piperine in rats. Moreover, the effect of piperine on the xenobiotic receptor constitutive androstane receptor (CAR) was further accessed.

KEY FINDINGS: Time-dependent inhibitory effect of piperine on carbamazepine metabolism was observed, with kinact and KI of 0.0153 min-1 and 18.34 μM for rat, and 0.0093 min-1 and 9.45 μM for human. Based on such in-vitro metabolic parameters, further estimation using mechanistic static model indicated that piperine could increase the AUC of CBZ by 7% and 11% in rat and human, respectively. Significant inhibition on rat liver microsomal activity, Cyp3a2 mRNA and protein expression, CAR mRNA were demonstrated with piperine at 35 mg/kg. Yet, no direct effect on the activity of CAR for piperine was found.

SIGNIFICANCE: We have demonstrated the time-dependent inhibition by piperine on carbamazepine metabolism as the interaction mechanism. Prolonged use of piperine at high dose could increase carbamazepine concentrations through inhibiting metabolic enzyme activities and

their related genes expressions.

For full text, please **click here**.

Original Article:

Lai JC, Rahimi R, Verna EC, Kappus MR, **Dunn MA**, McAdams-DeMarco M, Haugen CE, Volk ML, Duarte-Rojo A, Ganger DR, O'leary JG, Dodge JL, Ladner D, Segev D. Frailty Associated With Waitlist Mortality Independent of Ascites and Hepatic Encephalopathy in a Multi-Center Study. Gastroenterology. 2019 Jan 17. pii: S0016-5085(19)30058-7. doi: 10.1053/j.gastro.2019.01.028. [Epub ahead of print] PubMed PMID: 30668935.

ABSTRACT

BACKGROUND & AIMS: Frailty is associated with mortality in patients with cirrhosis. We measured frailty using 3 simple tests and calculated Liver Frailty Index (LFI) scores for patients at multiple ambulatory centers. We investigated associations between LFI scores, ascites, and hepatic encephalopathy (HE) and mortality.

METHODS: Adults without hepatocellular carcinoma who were on the liver transplantation waitlist at 9 centers in the United States (N = 1044) were evaluated using the LFI; LFI scores of at least 4.5 indicated that patients were frail. We performed logistic regression analyses to assess associations between frailty and ascites or HE and competing risk regression analyses (with liver transplantation as the competing risk) to estimate sub-hazard ratios (sHRs) of waitlist mortality (death or removal from the waitlist).

RESULTS: Of study subjects, 36% had ascites, 41% had HE, and 25% were frail. The odds of frailty were higher for patients with ascites (adjusted odd ratio 1.56, 95% confidence interval [CI]

1.15-2.14) or HE (odd ratio 2.45, 95% CI 1.80-3.33) than for those without these features. Larger proportions of frail patients with ascites (29%) or HE (30%) died while on the waitlist compared with patients who were not frail (17% of patients with ascites and 20% with HE). In univariable analysis, ascites (sHR 1.52, 95% CI 1.14-2.05), HE (sHR 1.84, 95% CI 1.38-2.45), and frailty (sHR 2.38, 95% CI 1.77-3.20) were associated with waitlist mortality. In adjusted models, only frailty remained significantly associated with waitlist mortality (sHR 1.82, 95% CI 1.31-2.52); ascites and HE were not.

CONCLUSIONS: Frailty is a prevalent complication of cirrhosis that is observed more frequently in patients with ascites or HE and independently associated with waitlist mortality. LFI scores can be used to objectively quantify risk of death related to frailty-in excess of liver disease severity-in patients with cirrhosis.

For full text, please **click here**.

Original Article:
Perito ER, Mogul DB, VanDerwerken D, **Mazariegos G**, Bucuvalas J, Book L, Horslen S, Kim HB, Miloh T, Ng V, Reyes J, Rodriguez-Davalos MI, Valentino PL, Gentry S, Hsu E. The Impact of Increased Allocation Priority for Children Awaiting Liver Transplant: A Liver Simulated Allocation Model (LSAM) Analysis. J Pediatr Gastroenterol Nutr. 2019 Jan 31. doi: 10.1097/MPG.0000000000002287. [Epub ahead of print] PubMed PMID: 30720563.

ABSTRACT
OBJECTIVE: The aim of the study was to investigate the impact of prioritizing infants, children, adolescents, and the sickest adults (Status 1) for deceased donor livers. We compared outcomes under two "SharePeds" allocation schema, which prioritize children and

Status 1 adults for national sharing and enhanced access to pediatric donors or all donors younger than 35 years, to outcomes under the allocation plan approved by the Organ Procurement and Transplant Network in December 2017 (Organ Procurement and Transplantation Network [OPTN] 12-2017).

METHODS: The 2017 Liver Simulated Allocation Model and Scientific Registry of Transplant Recipients data on all US liver transplant candidates and liver offers 7/2013 to 6/2016 were used to predict waitlist deaths, transplants, and post-transplant deaths under the OPTN 12-2017 and SharePeds schema.

RESULTS: Prioritizing national sharing of pediatric donor livers with children (SharePeds 1) would decrease waitlist deaths for infants (<2 years, P=0.0003) and children (2-11 years, P=0.001), with no significant change for adults (P=0.13). Prioritizing national sharing of all younger than 35-year-old deceased donor livers with children and Status 1A adults (SharePeds 2) would decrease waitlist deaths for infants, children, and all Status 1A/B patients (P<0.0001 for each). SharePeds 1 and 2 would increase the number of liver transplants done in infants, children, and adolescents compared to the OPTN-2017 schema (P<0.00005 for all age groups). Both SharePeds schema would increase the percentage of pediatric livers transplanted into pediatric recipients.

CONCLUSIONS: Waitlist deaths could be significantly decreased, and liver transplants increased, for children and the sickest adults, by prioritizing children for pediatric livers and with broader national sharing of deceased donor livers.

For full text, please **click here**.

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