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FINAL

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SELECTION OF THE MONTH

Big title: NAFLD and coronary artery disease

Small title (Cirrhosis): Plectin and cholestasis

When achieving SVR is futile

Antiviral properties of toll-like receptor 7 agonists

ACUTE LIVER INJURY

Involvement of hepatocyte interleukin (IL)-1 receptor in early lipopolysaccharide (LPS)-induced liver injury

Among the 11 members of the IL-1 cytokine family there are IL-1 alpha, IL-1 beta and interleukin-1 receptor antagonist (IL-1ra) which are encoded by *IL1A*, *IL1B*, and *IL1RN*, respectively. IL-1 alpha and IL-1 beta exert their biological activities through the ubiquitously expressed IL-1 receptor type 1 (IL-1R-1; encoded by *IL1R1*). IL-1ra binds to IL-1R-1 to antagonize IL-1 alpha and IL-1 beta signaling. The role of IL-1R-1 in

hepatocytes during acute liver failure (ALF) being unknown, Gehrke *et al.* addressed this question leveraging a novel transgenic mouse model exhibiting deletion of all signaling-capable *Il1r* isoforms in hepatocytes (*Il1r1*Hep-/-). ALF was induced by a combination of LPS and D-galactosamine (D-GalN; a blocker of de novo LPS induction of prosurvival genes). Here, they show that **IL-1R-1 in hepatocytes plays a key role in an IL-1-driven, NALP3- and caspase 1-mediated auto-amplification of cell death and inflammation in the onset of ALF.**

ALCOHOLIC AND NON-ALCOHOLIC FATTY LIVER DISEASE

CAP to detect alcoholic steatosis and subclinical atherosclerosis in NAFLD

Controlled attenuation parameter (CAP) is a novel non-invasive measure of hepatic steatosis and is used along with elastrography (Fibroscan). In a study by Thiele *et al.*, 562 patients with biopsy-proven alcoholic liver disease were included from 4 detoxification centers in Europe. **CAP diagnosed steatosis with fair accuracy** (AUC ≥S1 = 0.77; ≥S2 = 0.78; S3 = 0.82). Importantly, CAP was superior to bright liver echo pattern by regular ultrasound. In the 293 patients who were admitted for detoxification, **CAP significantly decreased after a brief period of abstinence**. As expected, BMI predicted higher CAP, irrespective of drinking pattern. **Obese patients with BMI ≥30 kg/m^2 had a significantly higher CAP, which did not decrease significantly during detoxification**. This study demonstrates that CAP has a good diagnostic accuracy for diagnosing severe alcoholic liver steatosis and that the combination of obesity and alcoholic abuse have synergistic effects in causing steatosis. The fact that a short period of abstinence decreases steatosis suggest that simple steatosis is reversible also in alcoholic liver disease. Another important study in the field of NAFLD highlights the association with systemic cardiovascular problems. More specifically, a large study by Lee *et al*. investigated **the association between NAFLD and subclinical coronary atherosclerosis**. A total of 5,121 consecutive asymptomatic individuals with no prior history of coronary artery disease underwent abdominal ultrasonography and coronary computed tomography angiography (CCTA). Thirty-eight percent of the participants had ultrasonography- diagnosed NAFLD. **After adjustment for cardiovascular risk factors, odds ratios for any atherosclerotic plaque and non-calcified plaque were significantly higher in NAFLD**. In addition, there was a significant association of fatty liver index ≥30 with non-calcified plaque and NAFLD fibrosis score ≥-1.455 with non-calcified plaque. This relevant large epidemiological

study reveals that NAFLD was consistently associated with non- calcified plaque, suggesting an increased cardiovascular risk. These results confirm previous studies indicating that NAFLD is an important independent risk factor for atherosclerosis and cardiovascular disease. Further studies should determine whether performing CCTA is cost-effective in this population.

HEPATITIS C VIRUS (HCV) INFECTION

Eliminating HCV in Island by 2020, when achieving SVR is futile, antiviral treatment improves survival of HCV-infected patients on hemodialysis, DAA resistance revisited – no major concern anymore

The World Health Organisation (WHO) recently introduced a global hepatitis strategy aiming towards the elimination of hepatitis C and B by 2030. Some countries implemented strategies in order to achieve this goal as recently highlighted in the April issue of the *Journal* by Elsharkawy *et al.* who shared the experience with their Egyptian national hepatitis treatment program, the largest HCV elimination program ever performed. In high-income countries, however, in contrast to Egypt, injecting drug use represents the main driver for the ongoing HCV epidemiology. Using an elegant modelling approach, Scott *et al.* demonstrated that HCV elimination in Iceland is achievable by 2020 with some additional screening and treatment of persons who inject drugs (PWID). **The modelling suggests that a recently introduced treatment-as-prevention program, combined with an efficient healthcare system and high levels of community engagement, are likely to make Iceland one of the first countries to achieve HCV elimination**. If successful in achieving elimination, Iceland would become a real-world example of treatment-as-prevention for HCV that should be critically evaluated against modelling projections.

The high safety and efficacy of direct acting antivirals (DAAs) made it possible to treat practically all HCV-infected patients, irrespective of their disease stage, age, and comorbidities. However, eradicating the infection (i.e., inducing SVR) may not always positively impact patients' life expectancy, and this holds especially true for patients with decompensated cirrhosis, who remain at risk of cirrhosis-related outcomes, and those with severe comorbidities. The aim of the HepCom study was to elucidate the impact of comorbidities on the health outcomes after interferon (IFN)-free therapy-induced viral eradication in hepatitis C. **By combining the Charlson comorbidity index, age, and liver function (INR, albumin, and bilirubin), Ampuero *et al.***

developed a new tool (the HepCom score) to identify a very-high-risk group to die or suffer from relevant clinical events within the first two years of DAA treatment. This study provides relevant new insights for our management of HCV-infected patients with relevant comorbidities, and helps to define situations in which achieving SVR might be considered fairly futile.

A higher risk of developing chronic kidney disease (CKD) has been described in HCV-seropositive patients compared with seronegative ones, and HCV infection among patients on hemodialysis is associated with higher risk of death highlighting the urgent need for effective HCV treatment in this population. Before the advent of DAAs, however, among patients with chronic HCV infection on hemodialysis, only a minority had received antiviral treatment. The aim of the present study by Soderholm *et al.* was to describe the prevalence of CKD and hemodialysis among patients with chronic HCV infection in the nationwide Swedish registries, and to assess the effect of HCV therapy on survival in these patients. Among the HCV-infected population, 2.5% were diagnosed with CKD during 280,123 person-years, compared with 0.7% (1,454/202,694) in the matched general population resulting in a standardized incidence ratio of 4.0. In addition, the HCV cohort had an increased risk of being diagnosed with acute or unspecific kidney failure, kidney cancer, kidney transplantation, cryoglobulinemia, and diabetes mellitus. **The most striking finding of the present study was the significant survival benefit of treating HCV in chronically infected patients on hemodialysis, and that this benefit remained significant after controlling for age, acute kidney disease diagnosis, and kidney transplantation**. The clear message from this nationwide cohort study is to prioritize IFN-free treatment in HCV-infected patients with CKD with or without hemodialysis.

Second generation DAAs being more potent and less prone to resistance development have been recently approved to treat chronic HCV infection. Still concerns remain that certain naturally occurring baseline resistant variants may negatively impact treatment outcome. To evaluate the impact of baseline resistance-associated substitutions (RASs) on treatment outcome and emergence of RASs, Hezode *et al.* performed a large comprehensive analysis in 1,778 HCV GT1-6 infected patients treated with sofosbuvir plus velpatasvir within the ASTRAL 1-3, ASTRAL-5 and POLARIS-2-3 phase III studies. **Although the overall rate of NS5A class RASs at baseline was significant (28%, range 9% to 61% depending on genotype using a 15% sequencing assay cutoff), they did not impact SVR rates.** Only in HCV type 3,

slightly lower SVR rates were observed in patients with the *NS5A* RAS Y93H at baseline. Overall, the findings of this large scale study reassure the broad efficacy of second generation combination regimens across all genotypes independently of baseline RASs, and speak against the need for routine baseline resistance testing.

HEPATITIS B VIRUS (HBV) INFECTION

Unravelling how Toll-like receptor 7 agonists exert their antiviral properties

Targeting the innate immune system represents one of the different immunotherapeutic strategies against chronic HBV infection. GS-9620, a potent, orally active small molecule agonist of Toll-like receptor 7 (TLR7), is currently in clinical development for the treatment of chronic hepatitis B, and has previously shown to induce prolonged suppression of serum viral DNA and antigens in the chimpanzee and woodchuck HBV models. In this issue of the journal, two studies aimed to better characterize the molecular and immunomodulatory mechanisms underlying these antiviral effects. By using archived liver biopsies and paired PBMC samples from a previous chimpanzee study, Li *et al.* showed that GS-9620 treatment induced the expression of genes associated with HBV clearance and transiently induced intrahepatic lymphoid aggregates. **The data suggest that administration of an immunomodulatory agent can induce an effective antiviral CD8$^+$ T cell response despite HBV infection persisting for more than two decades**. In the second study, Niu *et al.* characterized the response of HBV-infected human hepatocytes (PHH) to GS-9620 and GS-9620-induced cytokines. **They demonstrated that GS-9620 had no direct antiviral activity but suppressed HBV RNA, DNA and antigens in HBV-infected PHH by the induction of type I IFNs in peripheral bold mononuclear cells**. Moreover, GS-9620-induced cytokines enhanced HBV antigen presentation. Both studies, provide important insights into the mechanisms underlying the antiviral response to TLR7 agonists in animal models of chronic HBV infection, but also have important implications for how HBV establishes chronicity, as well as for the therapeutic response to innate immune agonists.

CIRRHOSIS

Circulatory dysfunction and inflammation predicts mortality in cirrhosis

The recent recognition of acute on chronic liver failure as a distinct clinical condition and the role of systemic inflammation have led to a new hypothesis in which ‘systemic

inflammation' is proposed to play an important role in decompensation of cirrhosis. However, data supporting this hypothesis is currently lacking. The paper by Schepis *et al. i*s the first prospective study to address this question. The authors followed a large number of patients that underwent hepatic and systemic hemodynamic assessment and also measurement of C-reactive protein (CRP). **Their data provide clear evidence that systemic inflammation measured using CRP and cardiopulmonary hemodynamics are independent predictors of decompensation in previously compensated patients and, of mortality or need for liver transplantation in those with previously decompensated cirrhosis.** These data, if validated can be used clinically to risk-stratify patients to prevent decompensation.

CHOLESTASIS

The role of plectin in cholestasis

Biliary obstruction resulting in cholestasis leads to increased pressure in the biliary system and increased toxicity of bile. In order to compensate for this, the biliary epithelial cells and hepatic progenitor cells form a plexus of bile ductules around the portal veins. Intermediate filaments (IFs) are important in this biliary proliferation. Plectin (encoded by *PLEC*) is a ubiquitously expressed cytolinker that crosslinks IFs and anchors them at junctional complexes helping to maintain the dynamic properties of the cytoskeleton. The role of plectin in cholestasis is currently unknown. **Jirouskova *et al.* describe novel data of its role in *Plec* knock out mice that underwent bile duct ligation. Their data show for the first time that by plectin plays a critical role in protecting the liver from stress elicited by cholestasis by maintaining a proper keratin network and biliary epithelial stability.** These data have implications for understanding the pathophysiological basis of cholestatic diseases.

HEPATOCELLULAR CARCINOMA (HCC)-BASIC

Targeting intestinal translocation of bacterial byproduct to prevent the risk of HCC recurrence related to ischemia-reperfusion phenomenon following liver resection or transplantation

Cancer recurrence can occur after liver resection or liver transplantation for HCC. Liver graft ischemia-reperfusion (I/R) is a risk factor for HCC recurrence, but the involved mechanisms are unclear. Translocation of LPS (endotoxin; a pathogen-associated molecular pattern, PAMP) produced by intestinal Gram-negative bacteria and its

recognition by Toll-like receptor 4 (TLR4; an innate pattern-recognition receptor) is also known to promote liver carcinogenesis, highlighting the role of the gut-liver axis in HCC promotion. Orci *et al.* tested the hypothesis that mesenteric congestion due to portal blood flow interruption induces LPS-mediated TLR4 engagement, resulting in elevated liver cancer burden. They used different approaches including genetic and pharmacological inhibition of TLR4, gut sterilization. In addition, they assessed whether remote ischemic preconditioning (RIPC; induced by brief and repeated sequences of femoral vascular bundle clamping and de-clamping) could mitigate I/R-induced liver injury. Their results suggest that **modulation of the gut-liver axis and of the LPS-induced TLR4 response by RIPC, gut-sterilization and TLR4 antagonism represent potential therapeutic targets to prevent I/R lesions, and to decrease HCC recurrence after liver transplantation and resection.**

BILIARY TRACT CANCERS (BTCs)

Genomic landscape of BTCs, irradiation stent *vs.* uncovered self-expandable metallic stent for malignant biliary obstruction

BTCs are pathologically and clinically and heterogeneous and have poor response to treatments. Genomic profiling can improve understanding of their carcinogenesis, classification and provide new insights into treatment strategy. Nakagawa *et al.* performed large scale genome sequencing analyses on 412 BTCs (from Japan and Italy) to investigate their somatic and germline driver events and characterize their genomic landscape. BTCs included intrahepatic cholangiocarcinomas, distal cholangiocarcinomas, peri-hilar types (PHCs), and gallbladder or cystic duct cancers. They identified 32 significantly and commonly mutated genes including *TP53, KRAS, SMAD4, NF1, ARID1A, PBRM1,* and *ATR*, some of which negatively affected patient prognosis. A novel deletion of *MUC17* at 7q22.1 affected patient prognosis. Deleterious germline mutations of cancer-predisposing genes such as *BRCA1, BRCA2, RAD51D, MLH1*, or *MSH2* were detected in 11% of BTC patients. **These results indicate that BTCs have distinct genetic features including somatic events and germline predisposition.** These findings could be useful to establish treatment and diagnostic strategies for BTCs based on genetic information.

Placement of an irradiation stent has been demonstrated to offer longer patency and survival when compared to an uncovered self-expandable metallic stent (SEMS) in patients with unresectable malignant biliary obstruction. Zhu et al. aimed to further

assess the efficacy of an irradiation stent compared to an uncovered SEMS in those patients. They performed a randomized, open-label, parallel, trial of participants with unresectable malignant biliary obstruction at 20 centers in China. A total of 328 participants were randomly assigned to receive either the irradiation stent or the uncovered SEMS. Endpoints included stent patency (primary), technical success, relief of jaundice, overall survival, and complications. The results show that **better patency and longer survival can be achieved by insertion of an irradiation stent compared with an uncovered SEMS in patients with unresectable malignant biliary obstruction.**