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Richard Moreau*, Ramon Bataller, Thomas Berg, Jessica Zucmann-Rossi, Rajiv Jalan

Richard Moreau* at Centre de Recherche sur l'Inflammation (CRI), INSERM, Université Paris Diderot, Paris, France; DHU UNITY, Service d'Hépatologie, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France; Laboratoire d'Excellence (Labex) Inflamex, COMUE Sorbonne Paris Cité, Paris, France;*Corresponding author *E-mail address*: richard.moreau@inserm.fr

Ramon Bataller at Division of Gastroenterology, Hepatology and Nutrition University of Pittsburgh Medical Center, Pittsburgh, PA, USA.

Thomas Berg at Section Hepatology, Clinic for Gastroenterology and Rheumatology, University Hospital Leipzig, Leipzig, Germany.

Jessica Zucman-Rossi at Inserm UMR-674; Génomique Fonctionnelle des Tumeurs Solides; IUH; Paris, France; Université Paris Descartes; Labex Immuno-oncology; Faculté de Médecine; Sorbonne Paris Cité; Paris, France.

Rajiv Jalan at Liver Failure Group, Institute for Liver and Digestive Health, University College London, Royal Free Hospital, UK

SELECTION OF THE MONTH

Big Title: Gasdermin D: A new executor in NAFLD

Small Titles:

Cirrhosis: Sarcopenia: Independent predictor of mortality in cirrhosis

Subclinical atherosclerosis in NAFLD.

Extended treatment experience with tenofovir alafenamide (TAF)

Eliminating HCV in Egypt

LIVER REGENERATION

Liver organogenesis

Liver regeneration involves different types of liver cells, including hepatocytes and liver non-parenchymal cells (NPCs). However, the liver organogenetic mechanism, in particular the role of adult hepatocytes at ectopic sites, remains unknown. UtohI *et al.* addressed this important question using elegant mouse models with ectopic (kidney)

adult hepatocyte transplantation. **They show that hepatocytes alone play a leading role as organizer cells in liver organogenesis at ectopic sites via NPC recruitment.**

ACUTE LIVER FAILURE

Role of *Msr1* and NETosis in fulminant hepatitis (FH), balancing inflammatory responses in virus-induced FH

Macrophage scavenger receptor types I and II (short name: SR-A; encoded by *Msr1* in mouse) are membrane glycoproteins implicated in the pathologic deposition of cholesterol in arterial walls during atherogenesis. Two types of receptor subunits exist. These receptors mediate the endocytosis of a diverse group of macromolecules, including modified low density lipoproteins (LDL). SR-A is also known to be a pattern-recognition receptor which may play a role in the maintenance of immune homeostasis. *Msr1* is highly expressed in fetal and adult mouse livers. Moreover, *MSR1* is overexpressed in the livers of patients with FH. This is why Tang et al. investigated the role of *Msr1* in a mouse model of FH. Here, they reveal that ***Msr1* promotes virus-induced FH by inducing activation and release of neutrophil extracellular traps** (**NETs**), a process now known as **NETosis, and subsequent complement activation.** These promising results should be confirmed in human cases of FH.

Why some patients develop acute liver failure in the course of an acute hepatitis virus infection is not well understood, and it is unclear to which extent virus pathogenicity or immunopathology drives liver damage to this stage. In order to dissect the impact of locally induced type I IFN responses on myeloid cell function and hepatocytes during acute liver inflammation, Borst *et al.* performed elegant infection studies with two different DNA viruses, vaccinia virus and murine cytomegalovirus, which both encode several potent type I IFN evasion proteins and efficiently infect the liver and cause acute hepatitis. **The authors show that loss of IFN receptor leads to lack of control of viral infection followed by severe hepatic inflammation because Kupffer cells are not adequately replenished from the circulating monocyte pool.** The observation that type I IFN is a key player in balancing inflammatory myeloid cell function opens new perspectives for the therapy of acute viral hepatitis.

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 B VIRUS (HBV) INFECTION

Extended treatment experience with tenofovir alafenamide (TAF), antiviral treatment in HBV-associated intrahepatic cholangiocarcinoma (ICC)

TAF, a new prodrug of tenofovir, was recently approved by the FDA and EU to treat chronic HBV infection after week 48 results of two large phase III trials proved TAF as being comparably effective to TDF but without its potential side effects on kidney and bones. The interpretation of the results, however, was limited by the relatively short follow-up. This present week 96 findings of both international randomized double-bling phase III trials by Agarwal *et al.* confirm these earlier results. **Treatment with TAF resulted in a similar rate of viral suppression compared to that of TDF but with a superior safety profile of TAF relative to TDF regarding bone and renal parameters**. An intriguing finding was that the rate of ALT normalization was consistently higher for TAF than TDF, and although the mechanism of this effect remains yet unknown, it would be interesting to follow whether differences in the ALT response may influence long-term outcomes as for instance the risk of HCC development.

A recent meta-analysis demonstrated a close association between the incidence of HBV infection and ICC occurrence, but the impact of HBV infection on outcomes following resection of ICC has not been reported yet. In a large cohort of 928 consecutive Chinese patients with positive HBV surface antigen and/or HBV core antibody who underwent liver resection for histologically confirmed ICC Lei *et al.* examined the impact of HBV-DNA level and antiviral therapy on short- and long-term outcomes. **Main findings were that antiviral therapy initiated either before or after liver resection significantly decreased tumor recurrence and prolonged long-term survival.** The positive effect of antiviral therapy on tumor recurrence was, however, restricted to patients with high viral load and presenting with the cholangiolar type ICC, a type being reported to be more closely associated with HBV infection, and to have a better prognosis as compared to bile duct type ICC. Preoperative antiviral therapy also reduced viral reactivation as well as decreased resection-related morbidity. The inhibitory role of preoperative antiviral therapy on postoperative viral reactivation also contributed to a better short- and long-term survival. This study clearly suggests that antiviral therapy should be considered as an integral part in the management of patients with resectable ICC.

HEPATITIS C VIRUS (HCV) INFECTION

Eliminating HCV in Egypt, eight-week treatment duration revisited, patients' characteristics not treatment regimen determines HCC risk after SVR

In this issue of the journal Elsharkawy *et al.* share their experience with their **Egyptian national hepatitis treatment program, the largest HCV elimination program ever performed, which included a total of 337,042 patients** who started treatment from October 2014 till end of March 2016 in specialized treatment centers. Main lessons learned from the national HCV elimination plan were first, that a prioritization strategy focused on patients with advanced disease has his limitations leading to a significant backlog of patients waiting for treatment; second, post-treatment follow-up is difficult in limited resource settings but could be increased form less than 25% to 75% over time, and third, cheap generic DAAs are effective reaching SVR rates of approximately 97% and allow for expanding treatment programs in low and middle income countries. The Egyptian national program for treating hepatitis C can send several messages and share several limitations with countries of similar settings.

Shortening DAA treatment duration to 8 weeks has shown comparable cure rates in clinical trials in selected treatment-naïve patients without cirrhosis as compared to the standard 12-week regimen. However, its effectiveness under real-world conditions needs further confirmation. Aim of the present study by Buggish *et al.* was to compare the effectiveness and safety of an 8 or 12 week ledipasvir plus sofosbuvir (LDV/SOF) containing regimen in HCV type 1-infected patients treated in the large national real-world German Hepatitis C-Registry (DHC-R). Based on a data set of 2,404 patients, both the 8- and 12-week regimen achieved identical SVR rates. Relapse rates, however, were higher when the shorter 8-week regimen was applied to patients with cirrhosis, treatment experience, or HIV co-infection, emphasizing the importance of patient selection for the shorter treatment duration. **Overall, this large study provides strong evidence that a shorter 8-week LDV/SOF regimen is an optimal strategy as long as criteria for selecting the right patients were sufficiently taken into account.**

Being more sick when starting antiviral therapy, might be a likely explanation for the reported higher frequency of hepatocellular carcinoma (HCC) occurrence in patients with advanced liver disease, after receipt of interferon (IFN)-free therapy for HCV infection as compared to the observations obtained in the interferon era. Innes and colleagues used data from the Scottish HCV Clinical Database to study HCC-naïve individuals with liver cirrhosis receiving a course of antiviral therapy in Scotland from 1997-2016 resulting in a SVR. In univariate analysis, IFN-free receipt was indeed associated with a significantly increased HCC risk. However, after multivariate

adjustment for baseline factors like age, Child-Turcotte-Pugh score, and thrombocytopenia, no significant risk attributable to IFN-free therapy persisted. **This study clearly suggests that rather a change in patient case mix, and not the use of IFN-free therapy *per se*, accounts for the higher HCC incidence seen in patients with cirrhosis treated with DAAs**.

AUTOIMMUNE HEPATITIS

Transient elastography (TE) is useful in monitoring patients

At present, the decision to continue, alter the dose or stop immunosuppression in patients with autoimmune chronic active hepatitis (AICAH) is based upon clinical, immunologic and biochemical parameters. Hartl *et al.* provide intriguing and important data of the potential use of TE in patients with AICAH, primary biliary cholangitis and primary sclerosing cholangitis. **They correlated the results of biopsies with TE measurements and correlated these with clinical outcomes. The data showing that complete biochemical remission was a reliable predictor of a good prognosis in AIH and this is associated with fibrosis regression provides convincing evidence for the potential incorporation of TE measurements in the management of AICAH.**

HEPATOCELLULAR CARCINOMA (HCC)

LI-RADS *vs.* AASLD score for the non-invasive diagnosis of small HCC in high-risk patients

The Liver Imaging Reporting and Data System (LI-RADS) was developed by the American College of Radiology to standardize terminology and criteria for interpreting and reporting computed tomography (CT) and magnetic resonance (MR) imaging results of the liver in patients with a risk of HCC. The initial version of LI-RADS first appeared online in 2011 and has been updated several times. The aim of LI-RADS is to help radiologists categorize findings in at-risk populations and to assist referring physicians in understanding the reports of liver imaging. Observations are categorized from LR-1 (definitely benign) to LR-5 (definitely HCC). LI-RADS includes major and ancillary criteria. It has still not been determined how radiologists should use LI-RADS instead of AASLD criteria for the diagnosis of HCC in high-risk populations. Ronot *et al.* aimed to prospectively compare the diagnostic accuracy of AASLD and LI-RADS for the non-invasive diagnosis of small HCC using CT and MR imaging, and to evaluate

the diagnostic value of each ancillary feature of HCC found in LI-RADS. Between April 2009 and April 2012, they enrolled patients with cirrhosis and one to three 10-30 mm nodules to undergo CT and MR imaging. They now report their results which show that **the version 2014 of the LI-RADS is not more accurate than the AASLD score for the non-invasive diagnosis of small HCC in high-risk patients**. However, they suggest that LI-RADS can provide important and complementary information on the probability of having HCC in high risk patients allowing possible changes in management in these patients.

LIVER TRANSPLANTATION

Severity of sarcopenia adds to the MELD score in determining the risk of death and metabolomics allows donor-graft matching

Allocation of organs for liver transplantation uses the MELD score or its variations in many areas of the world. In recent years, there has been an increasing body of evidence that indicates that the severity of sarcopenia is important in the prognosis of cirrhotic patients. Vugt *et al.* performed and excellent study in over 500 from the European transplant registry and identified that about half of them had sarcopenia. **Analysis of the data revealed that the presence of sarcopenia, age and hepatic encephalopathy were independent risk factors for mortality. Addition of sarcopenia to MELD score significantly improved the identification of the risk of mortality over 3-months compared with MELD score.** With further validation, assessment of sarcopenia may enter routine clinical practice when attributing risk of mortality of cirrhotic patients.

At present, clinical scoring systems are used to identify the likelihood of poor graft function following liver transplantation leading often to the use of suboptimal organs for transplantation, rejection of organs likely to function well after transplantation and inappropriate donor-recipient matching. **Faitot *et al.* describe the results of a novel and exciting study where they used real-time magic-angle-spinning nuclear magnetic resonance (HR-MAS-NMR) metabolomic analysis of the back table biopsies from recipient and donors. Their results showing that the constructed model predicted the graft outcome with excellent accuracy.** The most significant differences were in lactate level and phosphocholine content. With further validation these data will allow better use of organs and perhaps provide new targets for therapy.