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FINAL

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SELECTION OF THE MONTH

Big Title: New model of HCC risk in NAFLD and ALD

Small Titles: When it comes to HCC prevention – are all HBV antivirals the same?
DAA in HCV-induced HCC – treat the tumor first
Burn associated cholestasis

LIVER MACROPHAGES

Fetal origin confers radio-resistance on liver macrophages

Cells of hematopoietic origin, including macrophages, are sensitive to radiation but a subset of Kupffer cells is radioresistant. Little is known on the identity of these different subsets of macrophages. This question was addressed by **Soysa *et al.*** who used elegant mouse models. Here, they show that the **murine liver exhibits a subset of Kupffer cells of embryonic origin which resists lethal irradiation through**

upregulation of cyclin-dependent kinase inhibitor 1 (encoded by *Cdkn1a*), and are maintained for a long period. In contrast, bone marrow-derived Kupffer cells do not survive lethal irradiation.

LIVER FIBROGENESIS

Hepatic stellate cells and portal fibroblasts contribute to cholestatic liver fibrosis

The cellular origin of extracellular matrix proteins in cholestatic disease is not well known. Hepatic myofibroblasts may originate from hepatic stellate cells (HSCs), portal fibroblasts (PFs) or fibrocytes. Their contribution to liver fibrosis may vary dependent on the etiology. In this issue, **Kisseleva *et al.*** investigated the composition of hepatic myofibroblasts in mice deleted for *Mdr2* (official gene symbol *Abcb4*), a well-described model that mimics primary sclerosing cholangitis, expressing a collagen-GFP reporter. **Activated PFs accounted for 26%, 51%, and 54% of collagen-GFP+ myofibroblasts in *Mdr2*$^{-/-}$ mice at 4 weeks, 8 weeks, and 16 weeks, respectively. The remaining collagen-GFP+ myofibroblasts were composed of activated HSCs**. In contrast, bone marrow-derived fibrocytes minimally contributed to liver fibrosis in *Mdr2*$^{-/-}$ mice. Interestingly, preventing oxidative stress induced by nicotinamide adenine dinucleotide phosphate oxidase (known as NOX) attenuated development of cholestatic fibrosis. This experimental study strongly suggests that both PFs and HSCs contribute to cholestatic-induced liver fibrosis and represent cellular targets for antifibrotic agents.

ALCOHOL-INDUCED LIVER DISEASE (ALD).

Natural History of biopsy-proven ALD.

The natural history of ALD is now well described. In this issue, **Parker *et al.*** performed a systematic review of most relevant published studies that followed-up patients with biopsy-proven ALD. Thirty-seven studies were included, reporting data from more than 7,500 patients. Amongst cohorts of heavy drinkers, 11% had normal histology, 28% had hepatic steatosis, 19% had steatohepatitis and 27% had cirrhosis. **The annual progression of pre-cirrhotic stage to cirrhosis were 1% in patients with normal histology, 3% in hepatic steatosis and 10% in patients with steatohepatitis. Annual mortality was 6% in patients with steatosis, 11% in steatohepatitis and 8% in cirrhosis**. Importantly, only in patients with steatosis did non-liver related mortality exceed liver-specific causes of mortality. This study reveals that a proportion

of heavy drinkers have silent cirrhosis and that steatohepatitis often evolves to cirrhosis and increases liver-related mortality. Campaigns aimed at detecting significant liver disease among heavy drinkers are urgently needed to prevent the progression to advance forms of liver disease. Early treatment of alcohol use disorders in these patients may reduce liver-related mortality.

GENETIC LIVER DISEASES

Genetic causes of hepatic iron overload detected by MRI

Iron overload is a major contributor to liver diseases. The genetic variants influencing liver iron content beyond the *HFE* gene are not well known. To identify new genetic variants, **Wilman *et al.*** performed a genome-wide association study in a study cohort including more than 8,000 individuals in whom hepatic iron content was quantified by RI and an independent cohort with 1,500 individuals. They identified **three independent genetic variants (rs1800562 in C282Y and rs1799945 in H63D in the *HFE* gene and rs855791 in *TMPRSS6*) associated with liver iron content**. The two HFE variants account for ~85% of all cases of hereditary hemochromatosis. Mendelian randomization analysis demonstrated that **central obesity plays a causal role in increased liver iron content**. Phenome-wide association analysis demonstrated shared etiopathogenic mechanisms for elevated liver iron and other systemic disease such as cirrhosis, hypertension and several malignancies. This massive genetic study provides genetic evidence that HFE variation accounts for the vast majority of cases with hepatic iron overload and that central obesity is associated with higher liver iron.

HEPATITIS B VIRUS (HBV) INFECTION

When it comes to HCC prevention – are all antivirals the same?

Although there is clear evidence that suppressing viral replication lowers the long-term risk of HCC development in HBV-infected patients, HCC occurrence cannot be completely prevented, remaining an unmet concern that need to be addressed in future treatment strategies. Whether the individual on-treatment HCC risk differs between the two most commonly used antivirals, namely the nucleoside analogue entecavir (ETV) or the nucleotide analogue tenofovir (TDF) has become a hot topic since a recent large scale Korean study provided evidence for a more pronounced HCC risk reduction in association with the use of TDF instead of ETV. In this issue of the journal Kim et al. expanded on this issue by recruiting 2.897 treatment-naïve Korean patients with

chronic hepatitis B who received ETV or TDF as a first line antiviral agent at four academic centres. **In contrast to a previous study from Korea, they found that the overall prognosis in terms of HCC development, need for liver transplantation, and death was not statistically different between patients treated with ETV vs. TDF**. Hence the jury is still open whether HCC risk reduction differs between different antiviral drugs and more controlled studies are needed to solve this clinically relevant question.

HEPATITIS C VIRUS (HCV) INFECTION

The PROs of DAA in real-world, DAA in HCV-induced HCC – treat the tumor first, RESOLVE the DAA failures in HIV/HCV coinfection

Patient-related outcomes (PROs) are increasingly used to gather information directly from the patients about their symptoms, and overall quality of life in the context of medical interventions, and stand in contrast to physician-reported outcomes, such as - in case of chronic hepatitis C - the induction of a sustained virologic response (SVR). PROs assessed in well controlled clinical trials evaluating direct-acting antivirals (DAAs) in patients with chronic hepatitis C overall significantly improve, especially in those achieving SVR, a finding that has been taken as another argument to come away from a solely disease severity-centered treatment approach. However, a comprehensive analysis of changes in PROs during and after DAA therapy in real-world clinical settings has not been performed. **Evon *et al.*** now for the first time collected large-scale comparative PRO data from a diverse U.S. multicenter observational study of 1601 HCV patients treated with DAAs developed by different pharmaceutical companies, including PRO data from patients who did and did not achieve SVR (PROP UP study). **Whereas overall PRO scores improved from baseline to post-treatment, with clinically meaningful improvements specifically in fatigue, sleep disturbance and functional well-being and these improvements were more pronounced in patients who achieved SVR, another important observation in this study was that one-quarter to one-third reported worsening of symptoms during DAA therapy**, depending on the regimen used. These findings have important implications for how clinicians might help set expectations with patients initiating DAA therapy, and providing a balanced perspective concerning changes of baseline symptoms and quality of life.

DAA treatment has become an integral part in the management of early stage HCV-induced HCC and inducing a SVR is associated with a survival benefit in this context. However, it is still debated whether the presence of a HCC may negatively impact the overall chance for getting SVR in comparison to patients without having this complication. In this issue of the Journal, **Ji *et al.*** performed a comprehensive meta-analysis including 49 studies from 15 countries, and comprising of 3341 and 35,701 patients with and without HCC, respectively to answer the question whether the presence and management of HCC impact DAA-induced SVR rates. **Although the meta-analysis clearly shows that the presence of HCC lowers the chance for SVR in comparison to the non-HCC population, this difference was mainly driven by patients who either received no or only palliative HCC treatments, whereas SVR rates were generally high in those treated curatively.** This finding lends further support for the effect of potential residual tumor contributing to the lower SVR rate observed in HCC patients and that HCC treatment should be considered prior to DAA therapy whenever possible.

The DAA triple regimen containing sofosbuvir plus velpatasvir and voxilaprevir (SOF/VEL/VOX) is recommended for all patients with DAA treatment failure and has shown excellent safety and efficacy in HCV mono-infected patents. Its efficacy in HIV/HCV co-infected patients suffering from a relapse after DAA treatment has not been studied yet. **Wilson *et al.*** presented the first data of its kind on the use of SOF/VEL/VOX for retreatment of HCV in HIV/HCV co-infection and/or those with non-compliance to prior treatment (The RESOLVE study). **The overall intention-to-treat efficacy of the DAA triple regimen was high and treatment response was neither affected by the presence of HIV co-infection nor by previous poor adherence to DAA-based therapy.** The data of this pilot study, evaluating for the first time SOF/VEL/VOX in HIV/HCV-co-infected patients and those with poor adherence, supports the use of this triple regimen in the retreatment in these special patient populations who failed to achieve SVR to previous DAA combinations.

HEPATITIS E VIRUS (HEV) INFECTION

HEV infection in hematologic malignancies – not an innocent bystander

HEV infection has become the leading cause among European patients with acute viral hepatitis. Although acute HEV infection usually has a benign self-limiting course in the absence of comorbidities, more severe forms and especially chronic infections can

occur in immunocompromised hosts. Patients with hematologic malignancies may represent a certain risk group for a more aggressive and chronic form of HEV infection and also being at an increased risk of HEV transmission via blood and blood products. However, as HEV infections in the context of hematologic malignancies have been understudied yet, **von Felden *et al.*** conducted a large retrospective, multi-center cohort study among different European centers to study the outcome of clinically overt hepatitis E cases in this special patient population. **The authors could clearly demonstrate that in patients with hematologic malignancies acute hepatitis E, which in 10% of all cases was transfusion associated, represents a relevant health threat leading to chronic infections, as well as acute and acute-on-chronic liver failure and death in a significant proportion of patients**. Early treatment initiation with ribavirin lowers HEV-associated mortality whereas reducing immunosuppressive treatment seems less promising. This study reminds us of the importance of HEV RNA screening in at risk populations and that we need to improve our preventive strategies in order to reduce the burden of hepatitis E in patients with hematologic malignancies.

CHOLESTASIS

Burn associated cholestasis (BAC) predicts poor outcomes

Cholestasis is commonly observed in patients with severe burns but whether this affects outcome is unknown. **Tymowski *et al.* present the results of one of the largest studies exploring the outcome of patients with severe burns to address this question. Their data clearly shows that the mortality of patients that developed BAC is about 2.5 times greater and was an independent predictor of death at 90-days.** BAC was associated with more severe burns, shock and infection. About 20% patients with BAC that recovered developed sclerosing cholangitis and continued to show evidence of cholestasis during follow up. The mechanisms surrounding these novel observations are unclear but add to the emerging data about critical care cholangiopathy.

CIRRHOSIS

Neurometabolic changes in a rodent model of cirrhosis

Although many lines of investigation have suggested an important role for ammonia in the pathogenesis of hepatic encephalopathy (HE), the sequence of metabolic brain

changes during the evolution of liver injury and cirrhosis is not known. In an important study, **Braissant *et al.* studied bile duct ligated rats longitudinally and monitored serial changes in neurometabolism using proton magnetic resonance spectroscopy. They show a progressive increase in brain glutamine and make the novel observation of a reduction in creatine and ascorbate with 2-3 weeks of bile-duct ligation.** They go on to show a good correlation between systemic hyperammonemia and brain glutamine levels and simultaneous changes in astrocyte morphology, providing further clear evidence of the ammonia-glutamine hypothesis of HE. The relevance of reduced creatine and ascorbate is unclear but may indicate new targets for neuroprotection.

HEPATOCELLULAR CARCINOMA (HCC) – CLINICAL

Modelling HCC risk, no effect on overall survival in advanced HCC with statin on the top of sorafenib, refining images of gadoxetate-enhanced MRI for diagnosis of early-stage cancer, nivolumab for sorafenib-experienced patients with HCC from Asia

HCC risk varies din patients with cirrhosis according to well-described, readily-available predictors. **Ioannou *et al.*** aimed to develop simple models estimating HCC risk in patients with alcoholic cirrhosis or nonalcoholic (NAFLD) cirrhosis and calculate the net benefit that would be derived by implementing HCC surveillance strategies based on HCC risk as predicted by our models. For this, they identified 7068 patients with nonalcoholic cirrhosis and 16,175 with alcoholic cirrhosis who received care in the Veterans Affairs healthcare system in 2012 and retrospectively followed them until January 2018 for the development of incident HCC. Next, they developed simple models estimating HCC risk in patients with one category of cirrhosis or the other, which are available as web-based tools (www.hccrisk.com). **They show that risk stratification can be used to inform risk-based HCC surveillance strategies in individual patients or healthcare systems or to identify high-risk patients for clinical trials.**

Although gadoxetate disodium-enhanced magnetic resonance imaging (MRI) has high sensitivity for diagnosis of HCC, its arterial-phase images may be unsatisfactory because of weak arterial enhancement. **Kim *et al.*** investigated the clinical effectiveness of arterial subtraction images from gadoxetate disodium-enhanced MRI for diagnosing early-stage HCC using the Liver Imaging Reporting and Data System

(LI-RADS) v2018. They now show that **arterial subtraction images of gadoxetate disodium-enhanced MRI can significantly improve the sensitivity for diagnosing early-stage HCC, without a significant decrease in specificity, using LI-RADS.**

Sorafenib is the reference palliative treatment for HCC. Combining sorafenib with another treatment to improve overall survival in the context of an acceptable safety profile, is still an unmet medical need. **Jouve *et al.*** hypothesized that statins may help to meet this medical need. They performed a randomized, parallel, open-label multicenter, phase 3 trial of sorafenib plus pravastatin versus sorafenib alone in patients with Child-Pugh class A cirrhosis and advanced HCC. The primary objective was overall survival. The results show that **adding pravastatin to sorafenib did not improve overall survival in patients with advanced HCC.**

Nivolumab is a monoclonal antibody against programmed cell death 1 and, therefore, is an immune checkpoint inhibitor. It is approved in several countries to treat sorafenib-experienced patients with HCC, based on results of trial named CheckMate 040 (a phase 1/2, open-label, non-comparative, dose escalation [USA, Spain, Hong Kong, and Singapore] and dose expansion [Canada, UK, Germany, Italy, Japan, South Korea, Taiwan] trial). However, marked differences exist in HCC clinical presentation, etiology, treatment patterns, and outcomes across regions. Yau et al. analyzed the safety and efficacy of nivolumab in the Asian cohort of CheckMate 040. Here they report that **nivolumab safety and efficacy are similar in Asian patients as compared with overall intention-to-treat population of sorafenib-experienced patients with HCC.**