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SELECTION OF THE MONTH
Immunogenicity of COVID-19 vaccination in patients with NAFLD and in liver transplant recipients

Despite the large number of clinical trials on COVID-19 vaccines, only a few participants with pre-existing liver diseases were included. In this issue of the Journal, 2 separate studies analyse the safety and efficacy of COVID-19 vaccines in patients with non-alcoholic fatty liver disease (NAFLD) and in liver transplant recipients. Wang et al. reported that neutralising antibodies against SARS-CoV were detected in 364 (95.5%) patients with NAFLD, based on an analysis of the CHESS2101 study from China. The authors concluded that vaccination is safe and effective in patients with NAFLD. Meanwhile, Rabinowich et al. assessed vaccine efficacy in liver transplant recipients and unfortunately found that immunogenicity among liver transplant recipients was very low with positive serology in only 47.5% of them, while antibody titre was also low in this group (mean 95.41AU/ml). This paper indicates that we may need to re-evaluate vaccine regimens in this population.

FROM THE EDITOR'S DESK
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EXPERIMENTAL AND TRANSLATIONAL HEPATOLOGY
FGFR2 fusions in cholangiocarcinoma models: new directions for combination therapy

Fibrolast growth factor receptor 2 (FGFR2) fusion proteins are found in about 15% of intrahepatic cholangiocarcinoma (iCCA) and most often occur together with additional mutations such as p53. From a clinical perspective, there is huge variability in responses to FGFR inhibitors. Cristinziano and coworkers used FGFR2 fusion protein-expressing mouse liver organoids and in vivo transplantation into mice to provide the conceptual framework for tackling this heterogeneity. While part of this heterogeneity depended on structurally different FGFR2 fusion proteins, dual blockade of FGFR2 fusions and the downstream effector Mek1/2 (by the clinically approved inhibitor trametinib) provided greater therapeutic efficacy than isolated inhibition of FGFR2 fusions. These insights from preclinical pharmacological targeting now await translation into personalised approaches in patients with iCCA.

Adipose-liver axis in NAFLD: succinate-driven inhibition of adipocyte lipolysis prevents lipotoxicity in fatty liver

Dysfunctional adipose tissue is a characteristic of patients with fatty liver disease, but molecular interactions between fat tissue and fatty liver are obscure. An and coworkers investigated the role of mitochondrial transporter, mitochondrial dicarboxylate carrier (mDIC) in white adipose tissue. mDIC mediates succinate transport from the mitochondrial matrix to the cytosol, where succinate can inhibit lipolysis and thereby reduces free fatty acid release from adipocytes to the liver. In mice lacking mDIC in adipocytes, high-fat diet feeding resulted in significantly exacerbated hepatic steatosis, inflammation, and fibrosis; in contrast, prolonged over-expression of mDIC in adipocytes substantially protected mice against hepatic steatosis, inflammation, and fibrosis. Understanding this molecular crosstalk between adipose tissue and liver metabolism may reveal new therapeutic avenues. Alcohol metabolism in liver sinusoidal endothelial cells contributes to alcohol-related liver diseases

Alcohol is metabolised in the liver by several pathways, including alcohol dehydrogenase 1 (ADH1) as well as cytochrome P450 2E1 (CYP2E1). Yang and coworkers identified that not only hepatocytes, but also liver sinusoidal endothelial cells (LSECs) express these enzymes and actively participate in alcohol metabolism. Using primary LSECs from rodents and humans as well as an ethanol injury model in mice, they demonstrate that alcohol metabolism by CYP2E1 in LSECs impairs endothelial functionality, which aggravates alcohol-induced liver injury in mice. These data suggest a yet unrecognised cellular target for interventions in alcohol-related liver diseases.

Regulation of bile acid synthesis as a target in cholestatic liver diseases

Bile acid (BA) synthesis and bile composition are disturbed in cholestatic liver diseases. Li and coworkers investigated the role of limb expression 1-like (LIX1L) protein in the regulation of bile salt homeostasis in patients, in vitro and in 2 mouse models of cholestasis. LIX1L is increased in cholestatic injury and can be stimulated in cells by culturing in the presence of BAs. In addition, the authors identified miRNA-191-3p as a regulator of LIX1L. Thus, the positive feedback loop of LIX1L and miRNA-191-3p for BA synthesis might be a target for the treatment of chronic cholestatic liver disease.

VIRAL HEPATITIS
Clinical efficacy of a novel, high-sensitivity HBcAg assay in the management of chronic hepatitis B and HBV reactivation

One of the clinically useful HBV markers, hepatitis B core-related antigen (HBcAg),
As the largest study with referral bias, the most important study is the one that explores a population of 664 individuals older than 45 years at average risk of colon cancer with known liver disease and low or no alcohol consumption, that is more characteristic of the general population than of patients seen in liver clinics. Patients were explored by an impressive array of imaging biomarkers: PDFF, MRE, elastometry, Multiscan CT1, and, in case any of the above were abnormal, by liver biopsy. Overall, the prevalence of NAFLD was 37.5% and of NASH 14%. Surprisingly 48% of individuals with a PDFF >5% had steatohepatitis in a large middle-aged US cohort. Most if not all studies on the prevalence of NASH are limited by tertiary care referral bias. Harrison et al. produced a major study which explores a population of 664 individuals older than 45 years at average risk of colon cancer with known liver disease and low or no alcohol consumption, that is more characteristic of the general population than of patients seen in liver clinics. Patients were explored by an impressive array of imaging biomarkers: PDFF, MRE, elastometry, Multiscan CT1, and, in case any of the above were abnormal, by liver biopsy. Overall, the prevalence of NAFLD was 37.5% and of NASH 14%. Surprisingly 48% of individuals with a PDFF >5% had steatohepatitis on biopsy. Importantly, 35% of individuals with NASH and 5.6% of those with NAFLD had significant fibrosis (≥F2). Steatofibrosis, i.e., bridging fibrosis without NASH was extremely rare, 1 case out of 10. Factors associated with NAFLD were: age, male sex, Hispanic race, diabetes and obesity. The study is important as it is the largest study with liver biopsy and modern imaging biomarkers in patients not selected for hepatology referral.

Prospective evaluation of the prevalence of non-alcoholic fatty liver disease and steatohepatitis in a large middle-aged US cohort

Muscle fat content is strongly associated with NASH in patients with morbid obesity

Current dogma stipulates that sarcopenia is associated with NAFLD, insulin resistance and the severity of fibrosis in non-alcoholic steatohepatitis (NASH). However, the role of other parameters such as myosteatosis has not been fully investigated. In a study by Nachit and Kwanten et al. on 184 morbidly obese patients, those with NAFLD had similar or higher muscle mass than those without NAFLD. Patients with more advanced liver disease (steatohepatitis with fibrosis) actually had an even higher muscle mass than patients with steatosis. However, there were large and unexpected differences in relation to muscle fat content of the psoas (myosteatosis). Myosteatosis was similar between patients with or without plain steatosis but was markedly higher in those with NASH. The association remained significant when multiple metabolic confounders were considered, including the amount of visceral fat and muscle insulin resistance. There was however no increase in patients with more active or more fibrotic NASH. After a dietary intervention or bariatric surgery, patients with NASH improvement had a significant decrease in myosteatosis. In fact, an 11% reduction in myosteatosis predicted NASH improvement with 100% specificity in this rather small series of patients with intervention and follow-up biopsy. Improvement in NASH activity but not fibrosis was associated with a reduction in myosteatosis. These provocative findings suggest that a high muscle fat content rather than a low muscle mass contributes to NAFLD progression, in particular the development of inflammation and hepatic cell injury.
AUTOIMMUNE LIVER DISEASES
Towards personalised medicine in autoimmune hepatitis
Candels et al. aimed to study whether treating autoimmune hepatitis with thiopurines (azathioprine or 6 mercaptopurine) with dose adjustments based on measurement of thiopurine metabolites is preferable to using traditional, standardised weight-based management. In this retrospective series, 109 patients had thiopurine metabolites (6-thioguanine, 6-methylmercaptopurine) and thiopurine methyl transferase activity measured as part of their management while 105 age- and sex-matched controls did not. Patients with metabolite measurements had higher rates of biochemical remission (77% vs. 60%) with a lower mean prednisone dose. Despite subtherapeutic TGN levels (i.e. lower than the range established for inflammatory bowel disease), a high proportion of patients remained in biochemical remission with fewer adverse effects. The authors conclude that metabolite measurements can help optimise treatment regimens in autoimmune hepatitis, as well as reduce adverse events and prevent failure to achieve/loss of biochemical remission. Based on these results they recommend metabolite dosing in patients with AIH who are failing to respond to treatment regimens in autoimmune hepatitis, particularly when biochemistry is unchanged or improving.

Single-cell atlas of hepatic T cells reveals expansion of liver-resident naive-like CD4+ T cells in primary sclerosing cholangitis
The understanding of autoimmune diseases requires the analysis of affected tissue, which harbours infiltrating and tissue-resident immune cells as well as their target cells, in a disease-specific microenvironment. However, few studies analysed the intrahepatic T cell compartment in primary sclerosing cholangitis (PSC). Poch et al. acquired single-cell sequencing data from 4 healthy donors and 11 livers with PSC and peripheral blood of the same patients, in parallel, to perform intra-individual analyses of intrahepatic and circulating T cells. They report on the first T cell atlas in PSC. The authors identified a previously unrecognised population of intrahepatic naive-like CD4+ T cells which was expanded in livers of patients with PSC and prone to develop a T(H)17 polarization state. Epigenetic imprinting contributed to the propensity to develop into T(H)17 cells. These cells located around the biliary ducts display a gene signature accounting for tissue residency. Interestingly, circulating CD4 T cells also show a higher capacity to acquire T(H)17-associated effector functions. By creating the first atlas of intrahepatic T cells the authors render naive CD4+ T cells likely contributors to the pathogenesis of PSC. Future research should determine whether intestinal or biliary microbiota are involved in the activation and differentiation of intrahepatic naive-like CD4+ T cells.

CIRRHOSIS
Bacterial infections in patients with acute variceal bleeding: an international multicentre study in the antibiotic prophylaxis era
In this study, Martínez et al. investigated the incidence and risk factors of bacterial infections during hospitalisation in patients with acute variceal bleeding (AVB) on antibiotic prophylaxis. The study is based on a post hoc analysis of the database of an international, multicentre, observational study designed to examine the role of preemptive transjugular intrahepatic porto-systemic shunt insertion in patients with cirrhosis and AVB. The primary outcome was the incidence of bacterial infection during hospitalisation. One-thousand six-hundred and fifty-six patients out of 1,770 (93.6%) received antibiotic prophylaxis, the most frequently used being third-generation cephalosporins (76.2%) and quinolones (19.0%). Of these, 320 (19.3%) patients developed bacterial infection during hospitalisation. Respiratory infection accounted for 43.6% of infections and for 49.7% of infected patients, and occurred early after admission. On multivariate analysis, respiratory infection was independently associated with Child-Pugh C, grade III-IV encephalopathy, orotracheal intubation for endoscopy, nasogastric tube, or oesophageal balloon tamponade. Thus, the authors stated that bacterial infections develop in almost one-fifth of patients with AVB despite antibiotic prophylaxis. Respiratory infection is the most frequent and is an early event after admission.

DRUG-INDUCED LIVER INJURY
Elevated bilirubin, alkaline phosphatase at onset, and drug metabolism are associated with prolonged recovery of DILI
Drug-induced liver injury (DILI) usually resolves after the discontinuation of the culprit medication, however, time to recovery can vary among patients, with 6-12% of patients developing a chronic liver disease. In this study, Ashby et al. investigated clinical factors and drug properties as potential risk determinants that influence the time course for DILI recovery and developed a model to predict its trajectory. The authors developed a multivariate recovery score model in 294 cases collected by the International Drug-Induced Liver Network Consortium (iDILIC) and then, they validated it in 257 cases from the Spanish DILI registry and 191 cases from the LiverTox database. A higher serum bilirubin and alkaline phosphatase at DILI onset, a longer time to onset, and non-significant liver drug metabolism were associated with a longer recovery and were included in a recovery score model. According to this model, high- and low-risk groups were identified. The estimated probability of recovery by 6 months was 0.46 (95% CI 0.26-0.61) for the high-risk group and 0.93 (95% CI 0.58-0.99) for the low-risk group in the iDILIC. Model performance was validated in both validation sets. The high- and low-risk cases identified by the model showed a different time course for recovery, with most low-risk cases recovering sooner. Thus, the authors concluded that this recovery score can be used to predict the trajectory of the patient’s recovery after culprit drug discontinuation so that, when a significant delay is predicted, clinicians may consider a deeper diagnostic work-up and/or an extended follow-up.

A novel microRNA-based prognostic model outperforms standard prognostic models in acetaminophen-induced acute liver failure
Acetaminophen (APAP)-induced acute liver failure (ALF) remains the commonest cause of ALF in the Western world. Conventional prognostic models utilising markers of liver injury and organ failure to predict mortality related to APAP-induced ALF lack sensitivity. Thus, Tavabie et al. aimed to develop a microRNA outcome prediction model for APAP-ALF, using a hepatic microRNA signature that has already shown to be associated with successful liver regeneration after post- auxiliary liver transplant and recovery from APAP-ALF. In a case-control study, serum samples from 194 patients with APAP-ALF enrolled in the US ALF Study Group registry (1998-2014) at early (day 1-2) and late (day 3-5) time-points were
used and a microRNA qPCR panel of 22 microRNAs was utilised to assess microRNA expression at both time-points. Multiple logistic regression was used to develop models which were compared to conventional prognostic models. Individual microRNAs confer limited prognostic value when utilised in isolation. However, incorporating them within outcome prediction models increases their clinical utility. A model containing regeneration-linked microRNA, model for end-stage liver disease (MELD) score and vasopressor use significantly outperformed commonly used outcome prediction models. Thus, the authors stated that a regeneration-linked microRNA signature combined with readily available clinical parameters can identify patients with poor prognosis who may benefit from transplantation.

HEPATIC AND BILIARY CANCER
FOSL1 contributes to the aggressiveness of cholangiocarcinoma and can be therapeutically targeted
Some molecular alterations are specific to intrahepatic or extrahepatic cholangiocarcinoma (CCA), while KRAS is mutated in both types in a significant proportion of patients. Transcriptional regulators including FOSL1 play a key role in cancer progression in some tumours and represent a vulnerability in lung and pancreatic cancer driven by oncogenic KRAS. Vallejo et al. have shown that FOSL1 is upregulated in CCA and that FOSL1 expression along with KRAS/BRAF mutations is associated with the worst prognosis. According to their study, FOSL1 expression is regulated by the KRAS oncogene and plays a key role in CCA development and progression. FOSL1 abrogation has a favourable effect in animal models and the inhibition of FOSL1 effectors like HMGCS1 or AURKA using targeted agents including mTOR inhibitors was effective in arresting tumour growth. This provides a rationale for therapeutic development in this tumour for which effective systemic therapies are urgently needed.

LIVER TRANSPLANTATION
A notable proportion of liver transplant candidates with alcohol-related cirrhosis can be delisted because of clinical improvement
Patients with alcohol-related decompensated cirrhosis can improve until recovery from decompensation, but the rate of such an improvement remains unclear. Pose et al. aimed to investigate the probability of recovery and delisting due to improvement in patients with alcohol-related decompensated cirrhosis on the waiting list for liver transplantation, by performing a registry-based, multicentre, retrospective study including all patients admitted to the waiting list in Catalonia, Spain between 2007 and 2018. One-thousand and one patients were included, 420 (37%) with alcohol-related decompensated cirrhosis of whom 36 (8.6%) were delisted after improvement at a median time of 29 months after waiting list registration. Lower MELD score, higher platelets and either female sex or lower height were independently associated with delisting due to improvement, while time of abstinence did not reach statistical significance in multivariate analysis ($p = 0.055$). Five years after delisting, the cumulative probability of remaining free from liver-related death or liver transplantation was 76%, similar to patients with HCV-decompensated cirrhosis delisted after improvement. Interestingly, women have a higher probability of being delisted after improvement, partially due to a lower early access to liver transplantation for height discrepancies. Early identification of patients with potential for improvement may avoid unnecessary transplants.