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SELECTION OF THE MONTH

Big Title: Novel therapy for alpha-1 antitrypsin deficiency

Small title:

Alcoholic hepatitis and ACLF

Occult HBV infection and the risk of HBV reactivation

Eight-week HCV treatment duration revisited

LIVER REGENERATION

Involvement of Yap1-TGFβ-dependent epithelial mesenchymal transition (EMT)

Chronic defect of mechanisms that promote effective replacement of dead hepatocytes may result in the replacement of functional hepatic parenchyma with fibrous scar and ultimately cirrhosis. Oh *et al.* hypothesized that effective regeneration of injured livers requires hepatocytes to evade the growth inhibitory actions of transforming growth

factor (TGF)-β. Using mouse models of liver regeneration, they show that **interactions between the TGF-β and Hippo-Yes-associated protein signaling pathways stimulate hepatocytes to undergo an EMT-like response that is necessary for them to grow in a TGF-β-enriched microenvironment and regenerate injured livers.**

FATTY LIVER DISEASES

A new model of NAFLD-induced liver fibrosis and bile acid dysregulation in alcoholic hepatitis.

NAFLD is an increasing cause of cirrhosis and HCC worldwide. The development of novel targeted therapies often requires preclinical studies in suitable models. Most existing diet-induced mouse models for NASH require 6 to 12 months to induce severe liver disease, which hampers preclinical studies. In this issue, Tsuchida *et al.* developed a **murine NASH model with rapid progression of extensive fibrosis and HCC by using a western diet combined with low dose weekly intraperitoneal carbon tetrachloride (CCl4).** This **new model produced stage 3 fibrosis at 12 weeks and HCC development at 24 weeks**. Furthermore, whole liver transcriptomic analysis indicated that dysregulated molecular pathways in this model were closely similar to those of human NASH. This new experimental tool could be very useful to perform preclinical drug studies in NAFLD-induced fibrosis and HCC. In another article from this issue of the *Journal*, Brandl *et al.* studied a well-characterized cohort of patients with alcoholic hepatitis. Alcoholic hepatitis is a life-threatening condition characterized by profound jaundice. The degree of histological cholestasis is associated with poor outcome and represents a potential mechanism for biomarker and drug discovery. The authors found that **total and conjugated bile acids are significantly increased in patients with alcoholic hepatitis compared with controls. In contrast, de novo bile acid synthesis is significantly decreased in alcoholic hepatitis patients**. Importantly, total and conjugated bile acids correlate positively with FGF19 serum levels and with disease severity (as assessed by MELD). Univariate analysis demonstrated significant associations between FGF19 and bilirubin levels. This study reveals that serum FGF19 and bile acids are significantly increased in patients with alcoholic hepatitis, while de novo bile acid synthesis is suppressed. Modulation of bile acid metabolism or signaling represent a promising approach to treat patients with this severe medical condition.

GENETIC LIVER DISEASES

A promising approach to treat alpha-1 antitrypsin deficiency in humans.

Alpha-1 antitrypsin deficiency (AATD) is a common genetic disorder causing chronic liver disease. The PiZ mutation results in misfolded alpha-1 antitrypsin protein (Z-AAT) leading to hepatocyte damage and progressive liver disease. It has been proposed that RNAi-based approaches silencing production of hepatic Z-AAT could be useful in these patients. In this issue, Turner *et al*. preformed two important studies. First, they conducted a **double-blind, randomized trial in healthy volunteers receiving escalating doses of the investigational agent ARC-AAT. The second study consisted in a randomized trial in 11 PiZZ genotype AATD patients who received ARC-AAT or placebo**. A dose-response in serum AAT reduction was observed at doses ≥ 4 mg/kg with similar relative reductions in PiZZ patients and healthy volunteers at 4mg/kg. The study was terminated early due to toxicity findings related to the delivery vehicle (ARC-EX1) seen in a non-human primate study. **The authors conclude that PiZZ and healthy volunteers responded similarly to ARC-AAT with a remarkable knockdown of hepatic AAT production**. This promising approach should be tested in future studies modifying the drug vehicle.

HEPATITIS C VIRUS (HCV) INFECTION

8 weeks G/P are enough to eradicate HCV in non-cirrhosis

The direct acting antivirals glecaprevir, an inhibitor of the NS3/4A protease and pibrentasvir, an NS5A inhibitor (G/P), were recently approved as pangenotypic regimen with high barrier against resistance to treat HCV genotype 1–6 infection for a duration of 8-16 weeks depending on HCV genotype, treatment experience and cirrhosis status. Shortening treatment duration to 8 weeks, however, may theoretically increase the risk of virologic relapse in certain subgroups. But large numbers of patients are probably needed to unravel minor differences in treatment outcome according to treatment duration. Puoti *et al.* conducted an integrated efficacy analysis of 2041 patients from nine phase II and III trials with HCV genotype 1-6 infection without cirrhosis treated with G/P for either 8 or 12 weeks and determined whether any baseline factors impacted achievement of SVR12. **In patients without cirrhosis, the G/P regimen given for 8 weeks achieved a 98% overall sustained virologic response rate (SVR), irrespective of baseline patient or viral characteristics and**

extending treatment duration for 4 additional weeks did not significantly increase the SVR. This large-scale retrospective pooled analysis clearly reinforces our current treatment practice, but it also fascinating in demonstrating, how easily a long-lasting chronic viral infection can be eradicated if the antiviral regimen is strong.

HEPATITIS B VIRUS (HBV) INFECTION

Biomarkers to predict rituximab-induced HBV reactivation; Droplet digital PCR – a new tool to quantify cccDNA in occult HBV infection, A validated easy to use HCC risk score for patients under antiviral treatment

Hepatitis B reactivation occurs in 10-30% of patients with resolved HBV infection under rituximab-based chemotherapy without prophylactic antiviral treatment. This is of special concern in HBV endemic areas where approximately 60% of the adult population has resolved HBV infection, and where health care resources are limited. As high anti-HBs levels may confer some protection against HBV reactivation in this setting, and quantitative anti-HBc levels have recently emerged as a new biomarker for disease activity, Yang *et al.* hypothesized that combining these biomarkers might allow for a better prediction of the individual reactivation risk. Out of the 197 patients with resolved HBV infection prospectively followed under rituximab-based chemotherapy without any antiviral prophylaxis, 12% developed HBV reactivation. **HBV reactivation was best predicted by the combination of both biomarkers, high anti-HBc (≥ 6.41 IU/mL), and low anti-HBs (<56.48 mIU/mL) levels at chemotherapy baseline (HR of 17.29)**. The identification of a high-risk group for HBV reactivation under rituximab-containing chemotherapy is of high importance especially in regions with limited medical resources in order to optimize preventive strategies.

Occult HBV infection (OBI), defined by the presence of liver HBV DNA in the absence of serum HBsAg is a well-known risk factor associated with for HBV reactivation but also long-term HCC risk. In clinical routine, the presence of anti-HBc in the absence of HBsAg is often taken as an OBI surrogate. In an elegant study, Caviglia *et al.* evaluated the livers of 100 anti-HBc positive transplant donors for total intrahepatic HBV DNA and for HBV covalently closed circular DNA (cccDNA) with a new in-house droplet digital PCR assay (ddPCR). **The replication competent cccDNA intermediate could be detected in only a quarter of the anti-HBc positive livers, a finding which likely explains the relatively low rate of HBV reactivation seen in anti-HBc-positive patients undergoing immunosuppressive therapy**. An intriguing correlation

between quantitative anti-HBc serum levels and the presence of intrahepatic HBV DNA and cccDNA was observed which indicates, in line with the above-mentioned study, that quantitative anti-HBc levels are a useful surrogate not only to predict the presence of OBI but also to discriminate the patients at highest risk of HBV reactivation, helping clinicians to individualize reactivation prophylaxis.

Long-term antiviral therapy reduces but does not abolish the risk of hepatocellular carcinoma (HCC) development in patients with chronic HBV infection. This study by Hsu *et al.* analyzed population-wide data from two independent healthcare systems in Taiwan (N=25,874) and Hong Kong (N=25,839) to establish and validate an easy to use risk score to predict individual HCC risk under entecavir and tenofovir treatment. Cirrhosis, age, male sex, and DM were the independent HCC risk factors in these populations, and were weighted to construct the **CAMD** (***C***irrhosis, ***A***ge, ***M***ale sex**,** and ***D***iabetes mellitus) **score**. **The CAMD score accurately stratifies patients into three distinct risk subgroups with 3-year cumulative HCC incidences of 0.27%, 2.40%, and 10.75% in patients with a CAMD score <8, 8-13, and >13 points, respectively**. This large-scale study, being the first that developed and validated a risk score for HCC by population-based data instead of selected samples may help, if confirmed, to harmonize globally HCC surveillance strategies in patients under long-term antiviral treatment.

ACUTE ALCOHOLIC HEPATITIS

Acute on chronic liver failure (ACLF) defines the risk of death in patients with acute alcoholic hepatitis (AH)

Treatment of alcoholic hepatitis is an unmet need. Mortality rates in patients with AH are high and the lack of risk stratification has made designing clinical trials difficult. In patients with acute deterioration, the occurrence of ACLF identifies a group of patients at high risk of death. **Sersté *et al.*** describe the results of an important study where they studied biopsy proven patients with AH to determine whether the presence of absence of ACLF was able to provide prognostic information. They then validated their findings using a second cohort of patients with probable AH. **Their data show for the first time that ACLF classification accurately stratifies patients with AH at high risk of mortality. The occurrence of infection identifies those at risk of developing ACLF.** Further validation of this concept is likely to allow better clinical management of AH patients and design of clinical trials.

ACUTE LIVER FAILURE

Lactate dehydrogenase (LDH) and pyruvate dehydrogenase complex (PDHC) are potential targets for therapy of acute liver failure (ALF)

Treatment of ALF is an unmet need and in patients fulfilling criteria for poor prognosis, the only treatment known to prolong life is liver transplantation. Over the past few years, it has become clear that metabolic enzymes can translocate to the nucleus and regulate gene expression through histone acetylation. **Ferreiro *et al.* describe for the first time convincing evidence of translocation of LDH and PDHC to the nucleus in animal models of ALF, provide proof of their role in acetylation of histones and go on to show incontrovertibly in 3 animals models that inhibiting these enzymes or using histone acyltransferase inhibitors significantly reduced the severity of liver injury.** These exciting new data provide novel targets of therapy for the treatment of ALF.

CIRRHOSIS

Spleen stiffness measurements (SSM) improves BAVENO-VI criteria for identification of high-risk varices

Variceal bleeding in patients with cirrhosis changes the natural history of the disease and recognition of patients at high risk of bleeding would allow institution of prophylactic strategies. Liver stiffness measurement (LSM) is a surrogate for the severity of portal hypertension and the addition of platelet count to the LSM has been proposed by BAVENO-VI as a screening tool. SSM has also been shown in previous studies to reflect the severity of portal hypertension. **Colecchia *et al.* added SSM to the BAVENO-VI criteria and show that this strategy significantly improves the performance of the model predicting the presence of high-risk varices.** Further validation of this important observation is likely to change the current guidance and further reduce the need to screening endoscopies.

PRIMARY SCLEROSING CHOLANGITIS (PSC)

Lysyl oxidase-like protein 2: A novel target of therapy of PSC

The clinical course of PSC is unpredictable and its treatment is an unmet need. The extracellular matrix protein, lysyl oxidase-like protein 2 (hereafter called LOXL2) is an important component of the extracellular matrix and is involved in it stabilization but its

origin, role in fibrosis and function in disease is not clear. **Pollheimer *et al.*** performed a series of elegant and extensive experiments using biliary epithelial cells (BECs), animal models and patients to address these questions. **Their data provide convincing evidence that LOXL2 is produced by reactive BECs and this is possibly responsible for an increase of tight junction permeability. They go on to show that pharmacological LOX-inhibition, in vitro ameliorates this defect arguing that anti-LOXL2 may be beneficial in PSC.** The data provide a potentially novel approach for treatment of PSC.

HEPATOCELLULAR CARCINOMA (HCC) CLINICAL

Dual-tracer PET/CT for staging, exploratory analysis of the RESORCE trial, newly diagnosed HCC in patients receiving DAAs

HCC staging according to the Barcelona Clinic Liver Classification (BCLC) classification is based on conventional imaging. Chalaye *et al.* performed a retrospective study in 177 patients with HCC, assessing the impact of dual-tracer, 18F-fluorocholine and 18F-fluorodeoxyglucose, positron emission tomography–computed tomography (PET/CT) on tumor staging and treatment allocation. They show that **using dual-tracer PET/CT for HCC staging, enabled BCLC upgrading and treatment modification in 11% and 14% of patients, respectively.** Dual-tracer PET/CT might also be useful in specific situations, including unexplained rise in α-fetoprotein, doubtful lesions or pre-transplant evaluation of patients without active HCC.

The RESORCE trial was a randomized, double-blind, parallel-group, placebo-controlled, phase 3 trial which showed that regorafenib improves overall survival in patients who had HCC progression while they were on sorafenib treatment. Finn *et al.* now report results of an exploratory analysis of 573 patients of the RESORCE trial, whose aim was to describe outcomes of sequential treatment with sorafenib followed by regorafenib. They show that **regorafenib is associated with a clinical benefit regardless of the last sorafenib dose or time-to-progression on prior sorafenib.** Of note, rates of adverse events are generally similar regardless of the last sorafenib dose.

Conflicting data have been reported on the risk of HCC during/after therapy with direct-acting antiviral agents (DAAs). Romano *et al.* aimed to evaluate incidence of newly diagnosed HCC and associated risk factors in patients with advanced hepatitis C,

treated with DAAs. The study was based on the NAVIGATORE platform, a prospectively recording database of all patients with hepatitis C receiving DAAs in Veneto region (Italy). Inclusion criteria were a fibrosis stage of F3 or more, according to METAVIR classification. Child-Pugh class C patients were excluded. The study included 3917 of 4234 consecutive patients; the mean follow-up was 1 year and a half. The results reveal that **among patients with advanced hepatitis C, those who were on DDAs and enrolled in this study, did not have a higher risk (and perhaps a lower risk) of developing 'de novo' HCC during the first year than those who were not treated and enrolled in previous studies.** The authors speculate that early HCC appearance may reflect pre-existing, microscopic, undetectable tumors.