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SELECTION OF THE MONTH

Big Title: HCV treatment allows transplant deactivation of 1 in 3 patients

Small title (Cirrhosis): Risk factors for chronicity of DILI

LIVER REGENERATION

A new marker for ductular reaction (DR)

The keratins are intermediate filament proteins responsible for the structural integrity of epithelial cells and are subdivided into cytokeratins and hair keratins. The type I cytokeratins consist of acidic proteins which are arranged in pairs of heterotypic keratin chains. The type II cytokeratins consist of basic or neutral proteins which are arranged in pairs of heterotypic keratin chains co-expressed during differentiation of simple and stratified epithelial tissues. Two members of the cytokeratin subfamily, i.e., keratin,

type I cytoskeletal 19 (K19, encoded by *KRT19*) and keratin, type II cytoskeletal 7 (K7, encoded by *KRT7*) are used as markers of the regenerative liver response termed DR which consists of activated biliary epithelial cells and hepatic progenitor cells and correlates with liver disease severity. Guldiken *et al.* now show that keratin, type I cytoskeletal 23 (K23, encoded by *KRT23*) is a stress-inducible marker of both DR and severity of liver disease. Interestingly, K23 is expressed in response to the type I acute-phase inducer interleukin (IL)-1 beta but not the type I inducer IL-6, suggesting some specificity. **These results suggest that K23 may serve as a marker for DR.**

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Non-invasive diagnosis, association with cardiovascular events and aggravation by sleep apnea

There is a clear need of optimizing non-invasive diagnosis of NAFLD. In this issue, Boursier *et al.* compared an array of **blood fibrosis tests as well as liver stiffness measurement (LSM) by Fibroscan** for the diagnosis of liver fibrosis and prognosis assessment in a large series of patients with biopsy-proven NAFLD. LSM and FibroMeter-V2G were the two best-performing tests in the cross-sectional study. Two fibrosis classifications were developed to precisely estimate the histological fibrosis stage using these two parameters. Importantly, the higher was the class of the fibrosis classification, the worse was the prognosis. This important clinical study shows that advanced liver fibrosis confers a worse prognosis in patients with NAFLD and that it can be accurately estimated by both LSM and novel serum markers. In another study in this issue, Targher *et al.* performed a **meta-analysis** to quantify the magnitude of the **association between NAFLD** (and NAFLD severity) and risk of **cardiovascular disease (CVD) events**. A total of 16 studies including 34,000 adult individuals and approximately 2,600 CVD outcomes over a median period of 7 years were included. Patients with NAFLD had a higher risk of fatal and/or non-fatal CVD events (OR: 1.64). Patients with more 'severe' NAFLD were also more likely to develop fatal and non-fatal CVD events (OR 2.58). This meta-analysis conforms that NAFLD is associated with an increased risk of fatal and non-fatal CVD events. At the clinical level, obesity-related **obstructive sleep apnea** (OSA) and nocturnal hypoxia are associated with NAFLD progression. Sundaram *et al.* studied if OSA/nocturnal hypoxia induced oxidative stress mediates this effect in **adolescents**. They found that the presence of OSA/hypoxia was associated with more severe fibrosis and urine **markers of**

oxidative stress. Moreover, markers of oxidative stress correlated with the degree of hypoxia. This study strongly suggests that OSA-associated hypoxia in young patients could exacerbate NAFLD by aggravating oxidative stress. Finally, this issue of the *Journal* includes a relevant study by Asgharpour *et al.*, who develop an **experimental model of NAASH-associated hepatocellular carcinoma** (HCC). A stable isogenic cross between C57BL/6J (B6) and 129S1/SvImJ (S129) mice were fed a high fat diet with ad lib consumption of glucose and fructose. Following initiation of the obesogenic diet, mice sequentially also developed steatosis (4-8 weeks), NASH (16-24 weeks), progressive fibrosis (16 weeks onwards) and **spontaneous HCC**. Importantly, the HCC gene signature resembled the S1 and S2 human subclasses of HCC. This novel model represents a unique opportunity for preclinical studies in NAFLD-associated HCC.

GENETIC LIVER DISEASES

UDCA as potential therapy for autosomic liver-kidney polycystic diasease

There are no effective pharmacological therapies for polycystic liver disease. Ursodeoxycholic acid (UDCA) attenuates experimental hepatic cystogenesis in vitro and in animal models of polycystic liver disease. On this background, D'Agnolo *et al.* conducted a multicenter randomized trial in symptomatic patients. Patients with symptomatic polycystic liver disease were randomly assigned to UDCA treatment (15-20mg/kg/day) or no treatment for 24 weeks. Primary endpoint was proportional change in total liver volume. The study revealed that **UDCA administration** for 24 weeks did not reduce **total liver volume** in all patients advanced PLD, while it r**educed it in the subset of patients with autosomal dominant polycystic liver-kidney disease**. This results merit further studies with larger number of patients.

HEPATITIS C VIRUS (HCV) INFECTION

Minimal residual viremia under sofosbuvir-based treatment - A concern?

Determining the time to first undetectable HCV RNA levels by close on-treatment monitoring of hepatitis C viremia was the corner stone for treatment individualization in the era of peg-interferon-based regimens. Whether viral kinetics measurement may be also of help to predict the risk of relapse under treatment with direct-acting antivirals (DAA) is unclear. In a network study of 3 European centers, Maasoumy *et al.* retrospectively correlated viral kinetics with treatment outcome in 298 patients with

HCV-genotypes 1-5 treated with sofosbuvir-based regimens. **Although residual HCV RNA was frequently detected at later stages of therapy**, and even in 20% of patients at the end of therapy, SVR-rates remained high in these patients and **this feature was not predictive for treatment failure**. Only in patients with HCV type 3 receiving the less robust sofosbuvir plus ribavirin regimen, the relapse rate was high, if HCV RNA levels exceed 45 IU/mL at week 2. Hence, even when hepatitis C viremia persists on-treatment at low levels, therapy should not be extended as long as patients receive robust dual DAA regimens.

HEPATITIS B VIRUS (HBV)

Therapeutic HBV vaccination? – not reached yet!

Hepatitis B virus (HBV) specific immune stimulation in patients under long-term nucleos(t)ide treatment (NUC) represents an interesting approach in order to increase HBsAg loss. GS-4774 is a heat-inactivated, yeast-based, T-cell vaccine that express HBsAg, hepatitis B core as well as X antigen, and in which the Sacchyaromyces cervisiae yeast component may act as a natural adjuvant, potentially allowing for new T-cell responses. In this controlled phase II "proof of concept study", Lok *et al.* randomized 178 patients with chronic HBV infection who were virally suppressed on an oral antiviral to continue NUC alone or receive NUC plus GS-4774 2, 10, or 40 yeast units subcutaneously every 4 weeks until week 20. **GS-4774 was well tolerated, but did not provide significant reductions in serum HBsAg in virally suppressed patients with chronic hepatitis B** and no patient experienced loss of serum HBsAg. Combination approaches with other agents, and evaluation in other populations of patients with HBV (i.e. treatment naive) are ongoing to determine if GS-4774 might have a therapeutic benefit.

HEPATITIS DELTA VIRUS (HDV)

Entry inhibition in chronic hepatitis D – a first step towards effective regimens?

Since the first description of a modest and mostly transient antiviral effect of interferon-based regimens in chronic hepatitis delta more than 20 years ago, no relevant improvement in the management of this most aggressive form of viral hepatitis has been achieved. In this issue, the pharmacokinetics as well as safety and efficacy of a novel HBV and HDV entry inhibitor, myrcludex B, was prospectively evaluated in two studies: first, an open first-in-human, phase I clinical trial in 36 healthy volunteers by

Blank A et al., and second, a phase Ib/IIa study in which 24 patients with chronic hepatitis delta were enrolled by Bogomolov P *et al.* Myrcludex B is a myristolated peptide of 47 amino acids derived from the preS1-domain of the HBV large surface protein that efficiently blocks entry of HBV and HDV. **This specific inhibition of the essential hepatic HBV and HDV virus receptor led to a reduction in HDV RNA in all patients,** and in 2 out of 8 patients under monotherapy and 5 out of 7 patients with combination therapy including peg-interferon HDV RNA became negative at treatment week 24. Longer follow-up is required to see the full effect of the compound and to judge its potential implications for the field. But so far, the data are encouraging, and do support further evaluation of myrcludex B in combination with peg-interferon in hepatitis B and D.

HEPATITIS E VIRUS (HEV)

Mechanisms of ribavirin resistance

Ribavirin has demonstrated significant antiviral activity against acute and chronic hepatitis E virus (HEV) infection. However, nonresponse to ribavirin may occur and has been linked to certain viral variants potentially conferring resistance to ribavirin. In an elegant study, Neyts *et al.* provide new insights in the mechanisms involved in ribavirin resistance showing that **certain mutations (Y1320H, K1383N and G1634R) in the viral polymerase (Y1320H, K1383N and G1634R), but also an insertion in the hypervariable region were associated with the ribavirin resistant phenotype**, and also play a role for viral fitness and replication efficacy. These data are highly relevant to better understand ribavirin resistance and the mode of ribavirin action in HEV infection.

HEPATOCELLULAR CARCINOMA (HCC)

Alcohol increases the risk of HCC

Whether alcohol intake increases the risk of complications in patients with HCV-related cirrhosis is debated. Vandenbulcke *et al.* addressed this question in a prospective observational study that enrolled 192 patients with compensated HCV-related cirrhosis. **They now show that light-to-moderate alcohol intake increases the risk of HCC in patients with HCV-related cirrhosis. These findings strongly suggest that patients' care should include measures to ensure abstinence.**

TRANSPLANTATION

HCV treatment allows transplant deactivation of 1 in 3

The introduction of oral DAA's has revolutionized the management of patients with HCV infection but the effect of HCV eradication using these drugs is unknown. Belli *et al.* analyzed the data of 103 HCV patients that were on the liver transplant waiting list in 11 transplant centers and treated with the oral DAAs. **This important study showed at 1 in 3 patients could be deactivated and 1 in 5 patients could be delisted over a 60-week period.** These results are very impressive but require more validation and establishing long term outcomes.

DRUG INDUCED LIVER INJURY

Identification of risk factors for chronicity in patients with DILI

Some patients who develop DILI end up with chronic liver disease but the risk factors associated with this are unknown. Lucena *et al.* studied the Spanish Registry for DILI and made some novel and important observations. Their data suggest that about 8% patients with DILI will develop chronic liver disease and that the term 'chronic DILI' should be used when the patients continue to show enzyme abnormalities at 1 year. About a third of these patients will develop cirrhosis. **The factors associated with chronicity are older age, the presence of dyslipidemia and more severe liver injury in month 2 after onset of DILI.** Very importantly, they identify the use of statins as being associated with chronicity.

CIRRHOSIS

A novel approach to analysis of EEG for possible diagnosis of minimal HE

The diagnosis of early grades of hepatic encephalopathy (HE) has been plagued with wide variability in the results of current tests, making it difficult to find clinically robust end-points and pathogenic mechanisms. Olesen *et al.* performed an important study focusing on variability of the EEG in cirrhotic patients. Although the variability of the EEG was lower in cirrhotic patients compared with controls, the data show a biphasic phenomenon in the cirrhotics. **In patients with minimal HE, the variability was increased compared with the unimpaired cirrhotic patients whereas it was decreased in those with overt HE.** The significance of this observation is unclear at present but provide provocative insight into the pathophysiological basis of HE.