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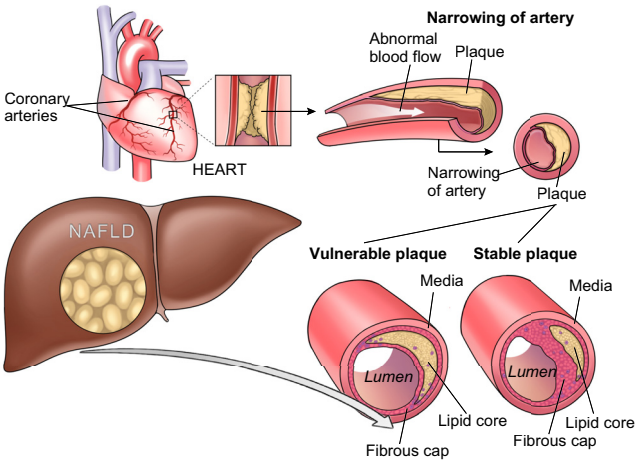
From the Editor's desk....

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

SELECTION OF THE MONTH

Subclinical atherosclerosis in NAFLD

An important study in the field of non-alcoholic fatty liver disease (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.



Lee *et al.*, 2018
Subclinical atherosclerosis in NAFLD.

ACUTE LIVER INJURY

Involvement of hepatocyte interleukin (IL)-1 receptor in early lipopolysaccharide (LPS)-induced liver injury

The 11 members of the IL-1 cytokine family include IL-1 alpha, IL-1 beta and interleukin-1 receptor antagonist (IL-1ra), which are encoded by *IL1A*, *IL1B*, and *IL1RN*, respectively. IL-1 alpha and IL-1 beta exert their biological activities through the ubiquitously expressed IL-1 receptor type 1 (IL-1R-1; encoded by *IL1R1*). IL-1ra binds to IL-1R-1 to antagonise IL-1 alpha and IL-1 beta signalling. The role of IL-1R-1 in hepatocytes during acute liver failure (ALF) is unknown Gehrke *et al.* addressed this by leveraging a novel transgenic mouse model in which all signalling-capable *Il1r* isoforms were deleted in hepatocytes ($Il1r1^{Hep-/-}$). ALF was induced by a combination of LPS and D-galactosamine (D-GalN; a blocker of *de novo* LPS induction of pro-survival genes). Therein, they show that **IL-1R-1 in hepatocytes plays a key role in an IL-1-driven, NALP3- and caspase 1-mediated auto-amplification of cell death and inflammation in the onset of ALF.**

ALCOHOLIC AND NON-ALCOHOLIC FATTY LIVER DISEASE

CAP to detect alcoholic steatosis

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 four detoxification centres 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 in alcoholic liver disease.

HEPATITIS C VIRUS (HCV) INFECTION

Eliminating HCV in Iceland by 2020, when achieving sustained virologic response (SVR) is futile, antiviral treatment improves survival of HCV-infected patients on haemodialysis, DAA resistance revisited – no major concern anymore

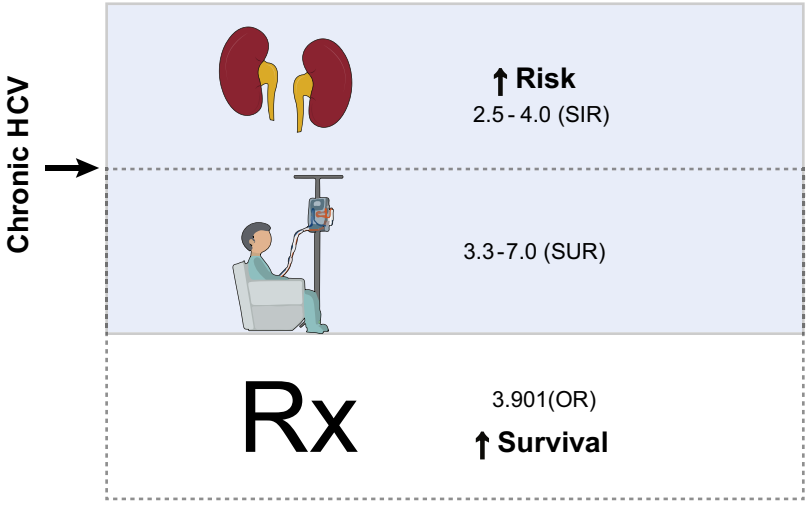
The World Health Organization recently introduced a global hepatitis strategy aiming towards the elimination of hepatitis C and B by 2030. Some countries implemented strategies to achieve this goal, as recently highlighted in the April issue of the *Journal* by Elsharkawy *et al.* who shared the experience with their Egyptian national hepatitis treatment programme, the largest HCV elimination programme ever performed. In high-income countries, however, in contrast to Egypt, injecting drug use represents the main driver for the ongoing HCV epidemiology. Using an elegant modelling approach, Scott *et al.* demonstrated that

HCV elimination in Iceland is achievable by 2020 with some additional screening and treatment of people who inject drugs. **The modelling suggests that a recently introduced treatment-as-prevention programme, combined with an efficient healthcare system and high levels of community engagement, are likely to make Iceland one of the first countries to achieve HCV elimination**. If successful in achieving elimination, Iceland would become a real-world example of treatment-as-prevention for HCV that should be critically evaluated against modelling projections.

The high safety and efficacy of direct acting antivirals (DAAs) made it possible to treat practically all HCV-infected patients, irrespective of their disease stage, age, and comorbidities. However, eradicating the infection (*i.e.*, inducing SVR) may not always positively impact patients' life expectancy, and this holds especially true for patients with decompensated cirrhosis, who remain at risk of cirrhosis-related outcomes, and those with severe comorbidities. The aim of the HepCom study was to elucidate the impact of comorbidities on the health outcomes after interferon (IFN)-free therapy-induced viral eradication in hepatitis C. **By combining the Charlson comorbidity index, age, and liver function (international normalized ratio, albumin, and bilirubin), Ampuero *et al.* developed a new tool (the HepCom score) to identify a group at very-high-risk of dying or suffering from relevant clinical events within the first two years of DAA treatment**. This study provides relevant new insights for our management of HCV-infected patients with relevant comorbidities, and helps to define situations in which achieving SVR might be considered fairly futile.

A higher risk of developing chronic kidney disease (CKD) has been described in HCV-seropositive patients compared with seronegative ones, and HCV infection among patients on haemodialysis is associated with higher risk of death, highlighting the urgent need for effective HCV treatment in this population. Before the advent of DAAs, however, among patients with chronic HCV infection on haemodialysis, only a minority had received antiviral treatment. The aim of the present study by Soderholm *et al.* was to describe the prevalence of CKD and haemodialysis among patients with chronic HCV infection in the nationwide Swedish registries, and to assess the effect of HCV therapy on survival in these patients. Among the HCV-infected population, 2.5% were diagnosed with CKD during 280,123 person-years, compared with 0.7% (1,454/202,694) in the matched general population resulting in a standardised incidence ratio of 4.0. In addition, the HCV cohort had an increased risk of being diagnosed with acute or unspecific kidney failure, kidney cancer, kidney transplantation, cryoglobulinemia, and diabetes mellitus. **The most striking finding of the present study was the significant survival benefit of treating HCV in chronically infected patients on haemodialysis, and that this benefit remained significant after controlling for age, acute kidney disease diagnosis, and kidney transplantation**. The clear message from this nationwide cohort study is to prioritise IFN-free treatment in HCV-infected patients with CKD with or without haemodialysis.

Second generation DAAs being more potent and less prone to resistance development have been recently approved to treat chronic HCV infection. Still concerns remain that certain naturally occurring baseline resistant variants may negatively impact treatment outcome. To evaluate the impact of baseline resistance-associated substitutions (RASs) on treatment outcome and emergence of RASs, Hezode *et al.* performed a large comprehensive analysis in 1,778 HCV GT1-6 infected patients treated with sofosbuvir plus velpatasvir within the ASTRAL 1-3, ASTRAL-5 and POLARIS-2-3 phase III studies. **Although the overall rate of NS5A class RASs at baseline was significant (28%, range 9% to 61% depending on genotype using a 15% sequencing assay cut-off), they did not impact SVR rates.** Only in HCV type 3, slightly lower SVR rates were observed in patients with the *NS5A* RAS Y93H at baseline. Overall, the findings of this large-scale study support the broad efficacy of second generation combination regimens across all genotypes independently of baseline RASs, and speak against the need for routine baseline resistance testing.



Soderholm *et al.*, 2018
Antiviral treatment improves survival of HCV-infected patients on haemodialysis

HEPATITIS B VIRUS (HBV) INFECTION

Unravelling how Toll-like receptor 7 agonists exert their antiviral properties

Targeting the innate immune system represents one of the different immunotherapeutic strategies against chronic HBV infection. GS-9620, a potent orally active small molecule agonist of Toll-like receptor 7 (TLR7) is currently in clinical development for the treatment of chronic hepatitis B, and has previously been shown to induce prolonged suppression of serum viral DNA and antigens in the chimpanzee and woodchuck HBV models. In this issue of the *Journal*, two studies aimed to better characterise the molecular and immunomodulatory mechanisms underlying these antiviral effects. By using archived liver biopsies and paired PBMC samples from a previous chimpanzee study, Li *et al.* showed that GS-9620 treatment induced the expression of genes associated with HBV clearance and transiently induced intrahepatic lymphoid