JOURNAL
OF HEPATOLOGY

From the Editor's desk....

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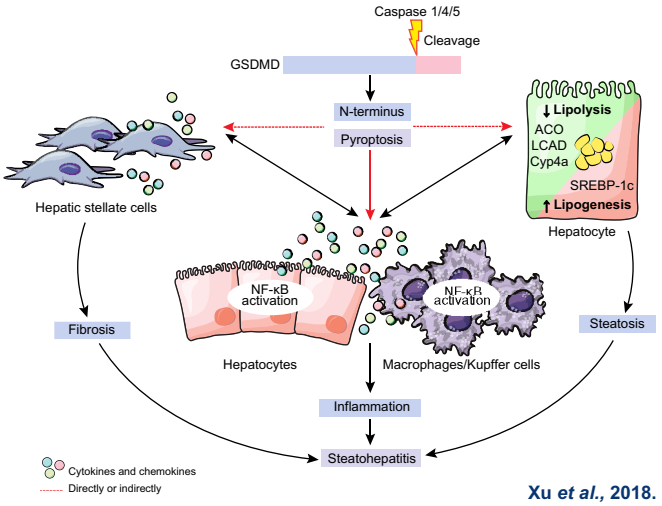
SELECTION OF THE MONTH

Hepatic pyroptosis in NASH

There is a clear need to identify molecular mechanisms of non-alcoholic steatohepatitis (NASH) to develop novel targeted therapies. Pyroptosis is a highly inflammatory form of programmed cell death. Gasdermin D (GSDMD)-executed programmed necrosis is involved in inflammation and controls interleukin (IL)-1β release. In this issue of the *Journal*, Xu *et al.* studied its role in human and experimental NASH. **GSDMD and its pyroptosis-inducing fragment GSDMD-N were upregulated in liver tissues of human NASH and correlated with disease severity**. *Gsdmd*$^{-/-}$ mice with experimental NASH exhibit decreased severity of steatosis and inflammation. GSDMD expression was associated with the secretion of pro-inflammatory cytokines and persistent activation of the NF-κB signaling pathway. Reduced steatosis in *Gsdmd*$^{-/-}$ mice was due to decreased expression of the lipogenic gene *Srebp*-1c and upregulated expression of lipolytic genes. This translational study reveals that **GSDMD plays a key role as a pyroptosis executor in the pathogenesis of steatohepatitis by controlling cytokine secretion and lipogenesis**.



Xu *et al.*, 2018.
Hepatic pyroptosis in NASH

LIVER REGENERATION

Liver organogenesis

Liver regeneration involves different types of liver cells, including hepatocytes and liver non-parenchymal cells (NPCs). However, the liver organogenetic mechanism, in particular the role of adult hepatocytes at ectopic sites, remains unknown. Utohl *et al.* addressed this important question using elegant mouse models with ectopic (kidney) adult hepatocyte transplantation. **They show that hepatocytes alone play a leading role as organiser cells in liver organogenesis at ectopic sites via NPC recruitment**.

ACUTE LIVER FAILURE

Role of *Msr1* and NETosis in fulminant hepatitis (FH), balancing inflammatory responses in virus-induced FH

Macrophage scavenger receptor types I and II (short name: SR-A; encoded by *Msr1* in mouse) are membrane glycoproteins implicated in the pathologic deposition of cholesterol in arterial walls during atherogenesis. Two types of receptor subunits exist. These receptors mediate the endocytosis of a diverse group of macromolecules, including modified low density lipoproteins. SR-A is also known to be a pattern-recognition receptor which may play a role in the maintenance of immune homeostasis. *Msr1* is highly expressed in foetal and adult mouse livers. Moreover, *MSR1* is overexpressed in the livers of patients with FH. This is why Tang *et al.* investigated the role of *Msr1* in a mouse model of FH. Here, they reveal that ***Msr1* promotes virus-induced FH by inducing activation and release of neutrophil extracellular traps (NETs)**, a process now known as **NETosis, and subsequent complement activation**. These promising results should be confirmed in human cases of FH.

Why some patients develop acute liver failure in the course of an acute hepatitis virus infection is not well understood, and it is unclear to what extent virus pathogenicity or immunopathology drives liver damage to this stage. In order to dissect the impact of locally induced type I IFN responses on myeloid cell function and hepatocytes during acute liver inflammation, Borst *et al.* performed elegant infection studies with two different DNA viruses, vaccinia virus and murine cytomegalovirus, which both encode several potent type I IFN evasion proteins and efficiently infect the liver and cause acute hepatitis. **The authors show that loss of IFN receptor leads to lack of control of viral infection followed by severe hepatic inflammation because Kupffer cells are not adequately replenished from the circulating monocyte pool**. The observation that type I IFN is a key player in balancing inflammatory myeloid cell function opens new perspectives for the therapy of acute viral hepatitis.

NON-ALCOHOLIC STEATOHEPATITIS

Diastolic heart dysfunction

An important study in this issue focuses on the link between NASH and increased cardiovascular risk. Myocardial function and its energy metabolism are tightly linked, which might be altered by an insulin resistant condition such as NAFLD. Lee *et al.* investigated whether hepatic steatosis and fibrosis were associated with myocardial dysfunction relative to myocardial glucose uptake. More than 300 patients (both with and without NAFLD) were studied. Compared to those without NAFLD, patients with **NAFLD had alterations in cardiac remodelling, manifested by increased left ventricle (LV) mass index, LV end-diastolic diameter, and LA volume index**. Hepatic steatosis was significantly associated with LV filling pressure (E/e' ratio), which reflects diastolic dysfunction. Those without NAFLD were more likely to have higher

myocardial glucose uptake compared to those with NAFLD. Moreover, significant hepatic fibrosis correlated with diastolic dysfunction and impaired myocardial glucose uptake. **Importantly, E/e' ratio was independently associated with hepatic fibrosis and steatosis**. This clinically relevant study demonstrates that hepatic steatosis and fibrosis are associated with diastolic heart dysfunction. Patients with progressive NAFLD should be evaluated for diastolic dysfunction if clinically indicated.

HEPATITIS B VIRUS (HBV) INFECTION

Extended treatment experience with tenofovir alafenamide (TAF), antiviral treatment in HBV-associated intrahepatic cholangiocarcinoma (ICC)

TAF, a new prodrug of tenofovir, was recently approved by the FDA and EU to treat chronic HBV infection after week 48 results of two large phase III trials proved TAF had similar efficacy to TDF, but without its potential side effects on kidney and bones. The interpretation of the results, however, was limited by the relatively short follow-up. The study by Agarwal *et al.* presents week 96 findings of both international randomised double-blind phase III trials, confirming these earlier results. **Treatment with TAF resulted in a similar rate of viral suppression as TDF, but with a superior safety profile regarding bone and renal parameters**. An intriguing finding was that the rate of alanine aminotransferase (ALT) normalisation was consistently higher for TAF than TDF, and although the mechanism of this effect remains unknown, it would be interesting to see whether differences in the ALT response may influence long-term outcomes, such as the risk of hepatocellular carcinoma (HCC) development.

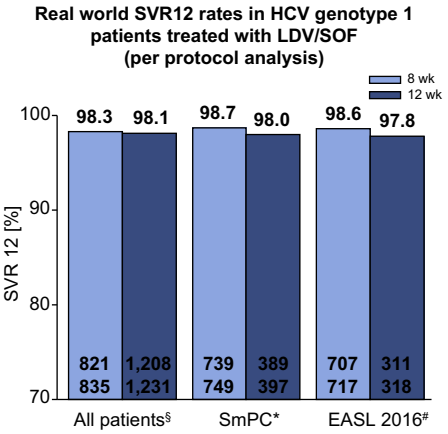
A recent meta-analysis demonstrated a close association between the incidence of HBV infection and ICC occurrence, but the impact of HBV infection on outcomes following resection of ICC has not been reported yet. In a large cohort of 928 consecutive Chinese patients with positive HBV surface antigen and/or HBV core antibody who underwent liver resection for histologically confirmed ICC Lei *et al.* examined the impact of HBV-DNA level and antiviral therapy on short- and long-term outcomes. **The main findings were that antiviral therapy initiated either before or after liver resection significantly decreased tumour recurrence and prolonged long-term survival**. The positive effect of antiviral therapy on tumour recurrence was, however, restricted to patients with high viral load and presenting with the cholangiolar type ICC, a type being reported to be more closely associated with HBV infection, and to have a better prognosis than bile duct type ICC. Preoperative antiviral therapy also reduced viral reactivation as well as decreasing resection-related morbidity. The inhibitory role of preoperative antiviral therapy on postoperative viral reactivation also contributed to a better short- and long-term survival. This study clearly suggests that antiviral therapy should be considered an integral part of the management of patients with resectable ICC.

HEPATITIS C VIRUS (HCV) INFECTION

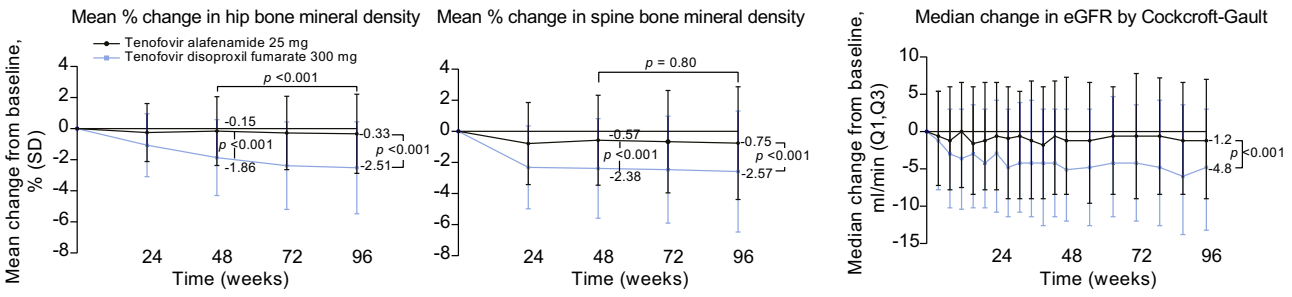
Eliminating HCV in Egypt, eight-week treatment duration revisited, patients' characteristics not treatment regimen determines HCC risk after sustained virologic response

In this issue of the journal Elsharkawy *et al.* share their experience with their **Egyptian national hepatitis treatment programme, the largest HCV elimination programme ever performed, which included a total of 337,042 patients** who started treatment from October 2014 until the end of March 2016 in specialised treatment centres. The main lessons learned from the national HCV elimination plan were first, that a prioritisation strategy focussed on patients with advanced disease has its limitations, leading to a significant backlog of patients waiting for treatment; second, post-treatment follow-up is difficult in limited resource settings but could be increased form less than 25% to 75% over time; and third, cheap generic DAAs are effective, reaching sustained virologic response (SVR) rates of approximately 97% and allow for expansion of treatment programmes in low and middle income countries. The Egyptian national programme for treating hepatitis C can send several messages and share several limitations with countries of similar settings.

Shortening DAA treatment duration to eight weeks has shown comparable cure rates in clinical trials in selected treatment-naïve patients without cirrhosis as compared to the standard 12-week regimen. However, its effectiveness under real-world conditions needs further confirmation. The aim of the present study by Buggisch *et al.* was to compare the effectiveness and safety of an 8- or 12-week ledipasvir plus sofosbuvir (LDV/SOF) containing regimen in patients infected with HCV type 1 in the large national real-world German Hepatitis C-Registry (DHC-R). Based on a data set of 2,404 patients, both the 8- and 12-week regimen achieved



Buggisch *et al.*, 2018
Eight week treatment duration revisted



Agarwal *et al.* 2018
Extended treatment experience with tenofovir alafenamide