JOURNAL
OF HEPATOLOGY

# From the Editor's Desk. . .

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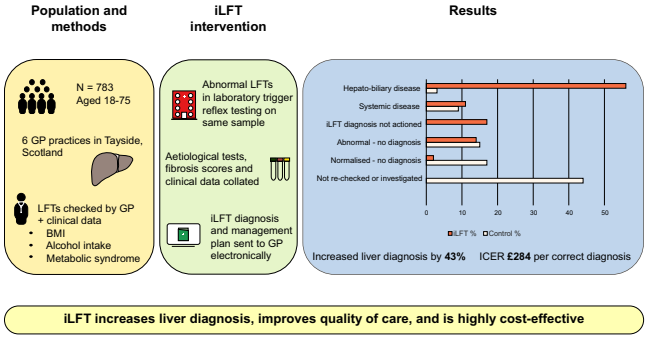
## SELECTION OF THE MONTH

### iLIFT: Ready to deploy in primary care?

The number of patients presenting to primary care with abnormal liver function tests or those that have risk factors for liver disease is increasing. Conventionally, in cases of abnormal liver function tests, a step-wise approach will be used, which has the potential to miss many patients with advanced liver disease. **Dillon *et al.* describe the results of an extremely important study in which they developed and tested the automated intelligent liver function testing (iLIFT) system, which integrates clinical and biochemical data, and provides recommendations and management plans.** They used a stepped-wedged trial design to evaluate this new system compared with conventional practice. Their data clearly show that the iLIFT system improved the diagnosis of advanced liver disease by 43%, whilst saving the health service approximately £3,216 per patient. If this system can be further validated, it is likely to change the way abnormal liver function tests are handled in primary care.




**Dillon *et al.*, 2019.**
iLIFT: Ready to deploy in primary care?

## NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

### Diabetes/prediabetes and the development of NAFLD in children/adolescents and global prevalence of NAFLD in T2DM

Alarmingly, the prevalence of NAFLD among children and adolescents is increasing worldwide. Factors associated with the development of NAFLD in this young population are only partially known. In this issue, **Nobili *et al.*** performed a large cross-sectional study of nearly 600 children/adolescents with and without NAFLD. The authors found that **patients with NAFLD had a significantly higher prevalence of abnormal glucose tolerance (prediabetes or diabetes)** than those without NAFLD (20.6% *vs.* 11%). The combined presence of prediabetes and diabetes was associated with a 2-fold increased risk of non-alcoholic steatohepatitis (NASH). Importantly, both the *PNPLA3* rs738409 polymorphism and waist circumference were associated with the development of NASH. This important study indicates that abnormal glucose tolerance (especially prediabetes) is highly prevalent among children/adolescents with biopsy-proven NAFLD and that **genetic and environmental factors (diet-induced central obesity) participate in the early development of fatty liver**. Campaigns promoting healthy lifestyle, especially among genetically predisposed children, are needed to reduce the burden of NAFLD among the young population. In another epidemiological study, **Younossi *et al.*** performed a systematic review to estimate the prevalence of NAFLD, NASH, and advanced fibrosis among patients with type 2 diabetes (T2DM) in 20 different countries across the world. **Among nearly 50,000 patients with T2DM, the overall prevalence of NAFLD was 55.5%**. Unexpectedly, studies from Europe reported the highest prevalence (68%). On the other hand, the overall prevalence of NASH was 37%. In a focused analysis, **advanced liver fibrosis was detected in 17% of patients with T2DM**. This important study provides an estimate of the global prevalence rates for NAFLD, NASH, and advanced fibrosis in patients with T2DM. These data can be used to model the potential prevalence of NAFLD and associated fibrosis in this common at-risk population.

## HEPATITIS B VIRUS (HBV) INFECTION

### sCD100 enhances HBV-specific CD8 T cell functions and HBV clearance

Clearance of HBV-infected hepatocytes is mainly driven by T cells which, however, show an exhausted phenotype in chronic infection. Unravelling the mechanisms involved in this HBV-associated immune dysregulation is critical for designing new immune-based treatment approaches. By promoting immune cell activation and responses, both membrane-bound mCD100 (also called Semaphorin-4D), mainly expressed abundantly on the surface of resting T cells, but also its soluble form (sCD100) which is cleaved from the cell surface by matrix metalloproteases, display important immune regulatory functions. By studying the role of CD100 in HBV clearance, **Yang *et al.*** demonstrated for the first time that chronic HBV infection does not only result in altered mCD100 expression and serum sCD100 levels but also that enhanced membrane CD100 shedding, and subsequent sCD100 formation, increases anti-HBV cytotoxic T lymphocyte responses and accelerates HBV clearance. **This study describes sCD100 as a potential new biomarker for evaluating the immune activation status in patients with chronic hepatitis B. sCD100 might also have potential as a therapeutic target in future treatment strategies**.

## HEPATITIS C VIRUS (HCV) INFECTION

### Treatment of DAA failure – certain risk groups may fail again; the safety of sofosbuvir in end-stage renal disease

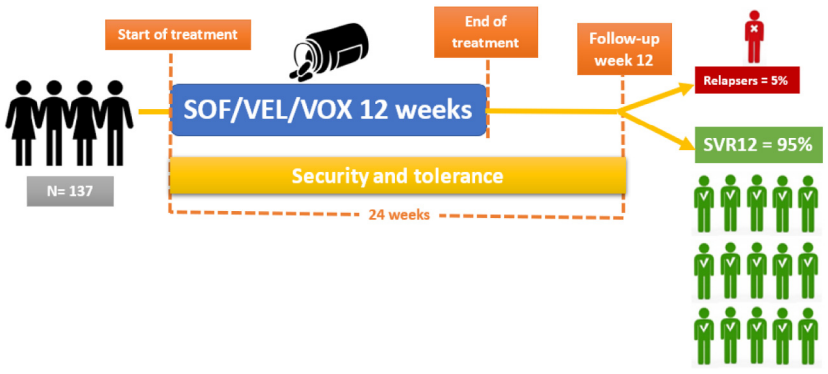
Failing antiviral treatment has fortunately become a rare event when treating chronic hepatitis C with current direct-acting antiviral (DAA)-based regimen. Although rare, the cumulative number of patients not achieving sustained virologic response (SVR) may ultimately become significant when considering the huge global epidemiological burden of this infection. A rescue approach with the triple DAA regimen containing sofosbuvir, velpatasvir and voxilaprevir (SOF/VEL/VOX) has demonstrated high efficacy in well-controlled phase III clinical trials, but its effectiveness in the real-world setting has not been sufficiently studied yet. **Llaneras *et al.*** conducted a large prospective multicentre study including previously DAA-treated patients who were retreated with SOF/VEL/VOX in Spain. **The overall SVR rates were high (95%), but in certain subgroups such as those with genotype 3 and cirrhosis they dropped as low as 69%.** The intriguing question arising from this first large real-world study that needs to be addressed further is whether cure rates can be improved in certain at-risk DAA failure populations by intensifying re-treatment, for instance by adding ribavirin.

Whether sofosbuvir-based regimens are safe in patients with end-stage renal disease (ESRD) is still highly debated but remains an important question as these regimens are the only ones that are recommended for patients with decompensated liver disease. Indeed, the predominant circulating metabolite of sofosbuvir, GS-331007, is renally cleared and accumulates in patients with severe renal impairment, being the reason that sofosbuvir-based regimens are not licensed in ESRD. The phase II multicentre study by **Borgia *et al.*** evaluated the safety and efficacy of sofosbuvir plus velpatasvir in patients with ESRD who were undergoing dialysis in order to expand our knowledge regarding the use of sofosbuvir-based regimens in these patient populations. **Although the plasma exposures of sofosbuvir, GS-331007, and velpatasvir were higher in HCV-infected patients with ESRD, the treatment regimen was well tolerated with no treatment-related discontinuations or serious adverse events, while an overall SVR rate of 95% was achieved**. Collectively, the data from this phase II study support the applicability of sofosbuvir plus velpatasvir as a safe, and highly effective treatment option for HCV-infected patients undergoing dialysis for ESRD.

## HEPATITIS E VIRUS (HEV) INFECTION

### HEV T cell receptor engineered T cells – a first step towards future T-cell based therapy

Ribavirin-resistant chronic HEV infection is associated with a significant risk of liver-related complications. Thus, alternative treatment concepts are urgently needed. Stimulated by recent immunotherapeutic approaches in HBV-related liver disease, **Soon *et al.*** investigated the possibility of generating HEV-cytotoxic T cells via the transfer of engineered T cell receptors (TCR), paving the way for the development of a HEV immunotherapy. **After identifying TCRs that target conserved HEV epitopes, this proof of concept study was able to demonstrate that TCR-redirected T cells from patients with chronic hepatitis E, who normally show no or low HEV-specific CD8+ T cell responses, were conferred with immunogenicity against epitope-loaded target cells**. Although this work is still in its infancy, as stated by the authors, it does represent an important step towards future developments into viable immunotherapy for patients with chronic HEV infection.



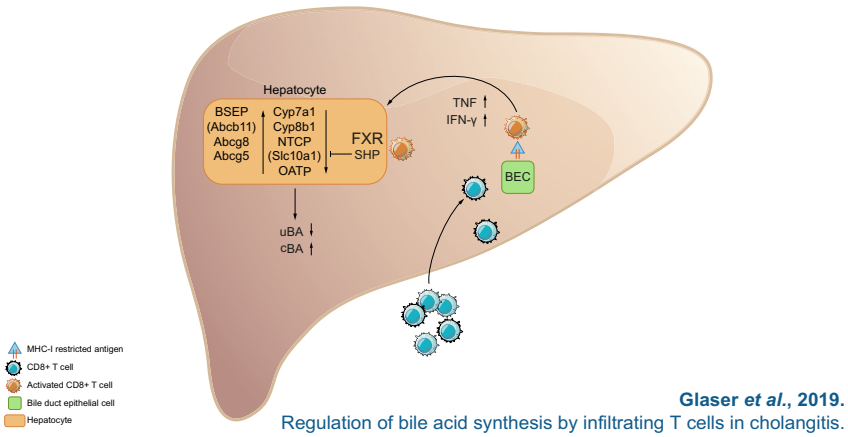

**Llaneras *et al.*, 2019.**
Treatment of DAA failure — certain risk groups may fail again.

## CHOLESTASIS

### IFNγ is important in the pathogenesis of sclerosing cholangitis, regulation of bile acid synthesis by infiltrating T cells in cholangitis

The pathogenesis of primary sclerosing cholangitis (PSC) is unknown. Considerable interest is focused on hepatic interferon-γ (IFNγ) producing lymphocytes. **Ravichandran *et al.* describe the results of an exciting study exploring the role of IFNγ in tissue biopsies from patients and also in animal models. Their results show increased levels of IFNγ in the serum of patients with PSC and also evidence of infiltration of the liver with natural killer cells.** Using multiple knock out animals and cell depletion techniques they showed convincingly that IFNγ changed the phenotype of the immune cells towards cytotoxicity and its absence attenuated the severity of liver injury, providing a potential novel therapeutic approach for patients with PSC.

It is well known that bile alters T cell function but whether T cells can alter bile acid metabolism is unknown. **Glaser *et al.*** explored this question in MDR knock out animals. **They produced T cell-induced cholangitis in these animals and showed that this resulted in low bile flow. They went on to show that this process was dependent on TNF and IFNγ in an FXR dependent manner.** These important data increase our understanding of the relationship between inflammation and bile acid metabolism, potentially enabling the development of new therapeutic strategies.




**Glaser *et al.*, 2019.**
Regulation of bile acid synthesis by infiltrating T cells in cholangitis.

## LIVER TRANSPLANTATION

### Is there a best system of organ allocation for transplantation? YAP activation: A therapeutic target to limit ischaemia-reperfusion injury

As the availability of organs for transplantation limits access of patients to liver transplantation, issues surrounding policies for allocation of organs become hugely important. It is clear that the practice of how organs are allocated varies from country to country. **Tsuchuor *et al.*** describe the results of a hugely important study where they evaluated the current world-wide practice of how liver allografts are allocated. **Their data confirm that the sickest first policy is the most reasonable strategy and that the MELD (model for end-stage liver disease) score is the most widely used, but with many country-specific adjustments.** They suggest that there is a need to develop a globally applicable strategy that combines donor and recipient factors to provide the best outcomes for patients on the waiting list and following liver transplantation.

Ischaemia-reperfusion injury exacerbates preservation injury and can result in delayed graft function or primary non-function. Many mechanisms have been postulated but have not been translated into clinical practice. **Liu *et al.*** describe the results of an impressive study where they show evidence of increasing YAP expression in human post liver transplant liver biopsies. **They went on to reproduce this in a murine model and then showed that activating YAP protected livers from injury, reduced synthesis of extracellular matrix proteins and diminished activation of hepatic stellate cells, whereas inhibiting YAP had the opposite effect.** Their data provide compelling evidence that YAP may be possible target to reduce the severity of ischaemia-reperfusion injury.

## CHOLANGIOCARCINOMA – TRANSLATIONAL

### Loss of Fbxw7 synergizes with AKT activation to promote c-Myc dependent carcinogenesis in cholangiocarcinoma, immune checkpoint molecules in cholangiocarcinoma

Although the ubiquitin ligase F-box and WD repeat domain-containing 7 (FBXW7) is recognized as a tumour suppressor in many cancer types due to its ability to promote the degradation of numerous oncogenic target proteins, its role in promoting intrahepatic cholangiocarcinoma is unknown. **Wang *et al.*** investigated this role in mouse models, intrahepatic cholangiocarcinoma cell lines, and human intrahepatic cholangiocarcinoma specimens. They show that **downregulation of FBXW7 is ubiquitous in human intrahepatic cholangiocarcinoma and cooperates with the protein kinase AKT to induce cholangiocarcinogenesis in mice via c-Myc-dependent mechanisms.** They speculated that targeting c-Myc might represent an innovative therapy against intrahepatic cholangiocarcinoma with low FBXW7 expression.

Whether cholangiocarcinoma is responsive to immune checkpoint antibody therapy is unknown, and little is known about its tumour immune microenvironment. **Zhou *et al.*** aimed to characterize tumour-infiltrating lymphocytes in cholangiocarcinoma and assess functional effects of targeting checkpoint molecules on these lymphocytes. For this, they isolated tumour-infiltrating lymphocytes from resected tumours of patients with cholangiocarcinoma and investigated their compositions compared with their counterparts in tumour-free liver tissues and blood, by flow cytometry and immunohistochemistry. They observed decreased numbers of cytotoxic immune cells and increased numbers of suppressor T cells with over-expression of co-inhibitory receptors in tumours, suggesting that the tumour microenvironment in cholangiocarcinoma is immunosuppressive. **They show that targeting immune checkpoint molecules such as GITR (glucocorticoid-induced TNF receptor), PD-1 (programmed death-1, also known as CD279), or CTLA-4 (cytotoxic T lymphocyte antigen-4, also known as CD152), enhances effector functions of tumour-infiltrating T cells**, suggesting that these molecules are potential immunotherapeutic targets for patients with cholangiocarcinoma.

## HEPATOCELLULAR CARCINOMA (HCC) – TRANSLATIONAL

### TLR3 downregulation promotes carcinogenesis in HCC, TOX promotes CD8 T cells exhaustion in HCC

Toll-like receptor (TLR) 3 is a pattern-recognition receptor located in the endosome where it recognises double-stranded RNA (non-self and self). Recognition of double-stranded RNA leads to a TRIF-mediated inflammatory response whose objective is to attract immune cells. Engagement of TLR3 in cancer cells has been shown to result in apoptosis of these cells. Because TLR3 levels are low in the livers from patients with HCC, **Bonnin *et al.*** addressed the hypothesis of a defect in TLR3-induced apoptosis in HCC cells (human and mouse HCC cell lines, and human surgically resected primary HCC tumours). They show that **downregulation of TLR3 protects transforming hepatocytes from direct TLR3-triggered apoptosis, an effect which can contribute to hepatocarcinogenesis.**

The thymocyte selection-associated high mobility group box protein (TOX) plays a vital role in T cell development and differentiation, and may play a role in T cell exhaustion. **Wang *et al.*** aimed to investigate the role of TOX in regulating the antitumor effect of CD8 T cells in HCC.

They sorted different subsets of CD8 T cells from human HCC. Their results reveal that **in HCC, TOX promotes CD8 T cell exhaustion (*i.e.*, a decrease in cytotoxic, antitumoral CD8 T cell action), by regulating endocytic recycling of PD-1.** Downregulating TOX expression in CD8 T cells exerts synergistic effects with anti-PD1 therapy, suggesting a promising strategy for immunotherapy in the context of HCC.

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