Significant fibrosis predicts new-onset diabetes mellitus and arterial hypertension in patients with NASH

Graphical abstract



Highlights

- NAFLD-related significant fibrosis predicts the occurrence of type 2 diabetes mellitus and arterial hypertension.
- The annual incidence of metabolic outcomes is four-times higher in the presence of significant fibrosis.
- Neither steatosis nor NASH predict the appearance of metabolic outcomes.
- Hepamet fibrosis score >0.12 is associated with the risk of developing type 2 diabetes mellitus.

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Lay summary

Patients with biopsy-proven non-alcoholic fatty liver disease and significant fibrosis were at risk of developing type 2 diabetes mellitus and arterial hypertension. The risk of metabolic outcomes in patients with significant fibrosis was increased in the presence of obesity. In addition to liver biopsy, patients at intermediate-to-high risk of significant fibrosis by Hepamet fibrosis score were at risk of type 2 diabetes mellitus.

Selonsertib for patients with bridging fibrosis or compensated cirrhosis due to NASH: Results from randomized phase III STELLAR trials

Graphical abstract



Highlights

- Selonsertib was safe and inhibited its target (ASK1) but did not lead to fibrosis regression or reduce disease progression in NASH.
- Improvement in liver fibrosis on biopsy was associated with improvement only in other histologic features.
- Improvements in ELF score and liver stiffness by transient elastography correlated with a variety of clinical parameters.

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Lay summary

Patients with non-alcoholic steatohepatitis (NASH) can develop scarring of the liver (fibrosis), including cirrhosis, which increases the risks of liver failure and liver cancer. We tested whether 48 weeks of treatment with selonsertib reduced fibrosis in patients with NASH and advanced liver scarring. We did not find that selonsertib reduced fibrosis in these patients.

Full-length 5'RACE identifies all major HBV transcripts in HBV-infected hepatocytes and patient serum

Graphical abstract



Authors

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Lay summary

Especially under infection conditions, it has been difficult to study the different hepatitis B virus transcripts in depth. This study introduces a new method that can be used in any standard lab to discriminate all hepatitis B viral transcripts in cell culture and in the serum of patients.

Highlights

- HBV full-length 5'RACE discriminates all viral transcripts including HBx.
- Viral particles contain pgRNA, pgRNA splice variants and different HBx RNAs.
- HBx RNAs in viral particles are both capped and uncapped.
- The composition of circulating viral RNA species can vary among patients.

Hepatitis B core-specific memory B cell responses associate with clinical parameters in patients with chronic HBV

Graphical abstract



Highlights

- B cell responses in chronic HBV are predominantly directed against HBcAg, not HBsAg.
- HBcAg-specific memory B cells associate with HBV's clinical phases.
- HBcAg-specific B cell responses are reduced during antiviral treatment.

Authors

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Lay summary

In recent years, studies examining the role of B cells during chronic hepatitis B virus infection have regained interest. We show that circulating B cells more often target the hepatitis B core antigen than the hepatitis surface antigen. Moreover, these hepatitis B core-specific B cells associate with the natural history of chronic HBV, and their responses decline during effective antiviral treatment.

Hepatitis B-related outcomes following direct-acting antiviral therapy in Taiwanese patients with chronic HBV/HCV co-infection

Graphical abstract



Highlights

- HBsAg levels decline during DAA therapy and rebound post-DAA therapy in HBV/HCV coinfected patients.
- HBsAg loss can occur in HBV/HCV coinfected patients on DAA therapy at a frequency seen in HBV monoinfection.
- HBV/HCV-coinfected patients are at risk of HBV reactivation after DAA, especially in those with higher HBsAg levels.
- HBV/HCV coinfected cirrhotic patients on DAAs should undergo HBV prophylaxis to reduce risk of hepatic failure and death.
- Quantitative HBsAg measurement could guide decision-making in HBV/HCV coinfected patients on DAA therapy.

Authors

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Lay summary

We studied outcomes relating to hepatitis B virus (HBV) in patients coinfected with both hepatitis B and C. Patients receiving direct-acting antiviral treatment for hepatitis C were more likely to experience seroclearance (or functional cure of HBV), but were also more likely to experience HBV reactivation, which can lead to hepatitis, liver failure and death. In coinfected cirrhotic patients being treated for HCV, prophylactic treatment for HBV is mandatory.

IFNL3-adjuvanted HCV DNA vaccine reduces regulatory T cell frequency and increases virus-specific T cell responses

Graphical abstract



Highlights

- DAAs successfully induce SVR in chronic HCV infection, but a prophylactic HCV vaccine is still warranted.
- We report here the first-in-human study demonstrating safety of an IFNL3-adjuvanted HCV DNA vaccine.
- IFNL3-adjuvanted HCV DNA vaccine reduces Treg cell frequency and increases virus-specific T-cell responses.
- *Ex vivo* IFN-λ3 treatment decreases Treg cell frequency in prevaccinated PBMCs, which might be an indirect effect by pDCs.

Authors

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Lay summary

Although direct-acting antivirals (DAAs) are successfully used for the treatment of chronic hepatitis C virus (HCV) infection, a prophylactic HCV vaccine needs to be developed, especially for patients who achieve a sustained virologic response. In the current study, we show that a DNA vaccine (GLS-6150) was safe and increased HCV-specific T cell responses. A clinical trial is underway to test this vaccine in patients with a sustained virologic response following DAA therapy.

Genotype correlates with the natural history of severe bile salt export pump deficiency

Graphical abstract



Highlights

- NAPPED is the largest global database of genotyped patients with BSEP deficiency.
- The genotype of patients with BSEP deficiency predicts survival with native liver.
- Genotype predicts long-term benefit of interruption of enterohepatic circulation.
- Serum bile acids can be a surrogate marker for long-term outcome.
- Treatment of patients with BSEP deficiency should be based on genotype.

Authors

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Lay summary

This study presents data from the largest genetically defined cohort of patients with severe bile salt export pump deficiency to date. The genotype of patients with severe bile salt export pump deficiency is associated with clinical outcomes and the success of therapeutic interventions. Therefore, genotypic data should be used to guide personalized clinical care throughout childhood and adulthood in patients with this disease.

A randomized, placebo-controlled, phase II study of obeticholic acid for primary sclerosing cholangitis

Graphical abstract



Highlights

- Novel treatments for PSC are an urgent unmet need.
- This phase II study evaluated OCA in patients with PSC.
- OCA 5–10 mg significantly reduced serum ALP levels at 24 weeks.
- The safety profile of OCA was consistent with previous studies.

Authors

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Lay summary

Primary sclerosing cholangitis (PSC) is a long-term disease that damages the bile ducts in the liver over time. In the AESOP clinical study in patients with PSC, obeticholic acid reduced serum alkaline phosphatase (a potential marker of disease severity) during an initial 24-week treatment period. The result was sustained during the 2-year, long-term extension of the study. The most common side effect of obeticholic acid in the study was itchy skin, which is consistent with earlier clinical studies.

Toll-like receptor 4 is a therapeutic target for prevention and treatment of liver failure

Graphical abstract



Highlights

- Cirrhosis is associated with TLR4-related sensitization to endotoxins and a switch from apoptotic to necroptotic cell death.
- Inhibition of TLR4 signaling by TAK-242 reduces immune cell responses and hepatocyte injury in response to LPS *in vitro*.
- In models of acute and acute-on-chronic liver failure, TAK-242 mitigated LPS-driven systemic inflammation and organ injury.

Authors

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Lay summary

Toll-like receptor 4 (or TLR4) mediates endotoxin-induced tissue injury in liver failure and cirrhosis. This receptor sensitizes cells to endotoxins, which are produced by gram-negative bacteria. Thus, inhibiting TLR4 signaling with an inhibitor (TAK-242) ameliorates organ injury and systemic inflammation in rodent models of acute and acute-on-chronic liver failure.

HDL-related biomarkers are robust predictors of survival in patients with chronic liver failure

Graphical abstract



Highlights

- HDL levels are profoundly decreased in chronic liver failure.
- HDL-related biomarkers (HDL-C, apoA-I) are robust predictors of disease progression and survival.
- The prognostic value of single HDL-related biomarkers is very similar to that of the composite scores.
- HDL-related biomarkers correlated inversely with markers of inflammation.

Authors

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Lay summary

People who suffer from cirrhosis (scarring of the liver) have low levels of cholesterol carried by high-density lipoproteins (HDL-C). These alterations are connected to inflammation, which is a problem in severe liver disease. Herein, we show that reduced levels of HDL-C and apolipoprotein A-I (apoA-I, the main protein carried by HDL) are closely linked to the severity of liver failure, its complications and survival. Both HDL-C and apoA-I can be easily measured in clinical laboratories and are as good as currently used prognostic scores calculated from several laboratory values by complex formulas.

Stereotactic body radiation therapy vs. radiofrequency ablation in Asian patients with hepatocellular carcinoma

Graphical abstract



Highlights

- SBRT provided better local control than RFA among patients with HCC.
- Toxicity rates and survival outcomes were similar between these treatment modalities.
- SBRT is an effective alternative to RFA for larger tumors (>3 cm) in a subphrenic location (especially segment 8).

Authors

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Lay summary

It is currently not known what the best treatment option is for patients with unresectable hepatocellular carcinoma. Here, we show that stereotactic body radiation therapy provides better local control than radiofrequency ablation, with comparable toxicities. Stereotactic body radiation therapy appears to be an effective alternative to radiofrequency ablation that should be considered when there is a higher risk of local recurrence or toxicity after radiofrequency ablation.

Portopulmonary hypertension in the current era of pulmonary hypertension management

Graphical abstract



Highlights

- Portopulmonary hypertension is a severe complication of portal hypertension.
- Therapies targeting pulmonary arterial hypertension improve cardiopulmonary haemodynamics.
- Combining these therapies and liver transplantation is associated with excellent long-term outcomes.

Authors

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Lay summary

Portopulmonary hypertension is defined by the presence of pulmonary arterial hypertension in the context of chronic liver disease and is characterized by progressive shortness of breath and exercise limitation. The presence of severe pulmonary arterial hypertension in liver transplant candidates represents a contraindication for such a surgery; however, treatments targeting pulmonary arterial hypertension are efficacious, allowing for safe transplantation and conferring good survival outcomes in those who undergo liver transplantation.

Exercise retards hepatocarcinogenesis in obese mice independently of weight control

Graphical abstract



Highlights

- Obesity and insulin resistance accelerate liver cancer onset in *foz/foz* mice.
- Mice with an in-cage exercise wheel engage in physical activity that abolishes the effect of obesity on hepatocarcinogenesis.
- Pair-fed *foz/foz* mice exhibit similar weight gain but are not protected.
- Exercise decreases proliferation of dysplastic hepatocytes by activating p53 to induce p27.
- A critical pathogenic role of JNK1 was also confirmed using *Jnk1^{-/-}.foz/foz* mice.

Authors

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Lay summary

Fatty liver disease commonly occurs alongside obesity and diabetes, contributing to rapidly increasing rates of liver cancer throughout the world.Herein.weshowthat exercise reduces the incidence and progression of hepatocellular carcinoma inmousemodels.Theeffect of exercise on cancer risk wasshowntobeindependent of changes in weight. Exercise could be a protective mechanism against liver cancer in at-risk individuals.

Hepatic stellate cell activation promotes alcoholinduced steatohepatitis through Igfbp3 and SerpinA12

Graphical abstract



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Lay summary

Hepatic stellate cells are known for their role in fibrosis (scarring of the liver). In this study, we describe their role in the modulation of fat deposition and inflammation in the liver, which occurs secondary to alcohol damage.

Highlights

- HSCs regulate hepatocyte steatosis that precedes liver fibrosis in alcohol-related liver disease.
- HSC-derived Igfbp3 and SerpinA12 mediate lipid droplet formation in hepatocytes.
- These results are recapitulated in samples from patients with alcoholic hepatitis.

[¹⁸F]-Alfatide PET imaging of integrin αvβ3 for the non-invasive quantification of liver fibrosis

Graphical abstract



Highlights

- [¹⁸F]-Alfatide was demonstrated to bind specifically with integrin $\alpha\nu\beta3$ (mainly expressed on activated HSCs).
- [¹⁸F]-Alfatide can detect fibrosis progression both in animal liver fibrotic models and human liver tissues.
- Imaging integrin $\alpha v\beta 3$ with PET/[¹⁸F]-Alfatide offers a potential non-invasive method for monitoring fibrosis progression.

Authors

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Lay summary

Integrin $\alpha\nu\beta$ 3 expression on activated hepatic stellate cells (aHSCs) is associated with HSC proliferation during hepatic fibrogenesis. Herein, we show that a radioactive tracer, [¹⁸F]-Alfatide, binds to integrin $\alpha\nu\beta$ 3 with high affinity and specificity. [¹⁸F]-Alfatide could thus be used as a noninvasive imaging biomarker to track hepatic fibrosis progression.