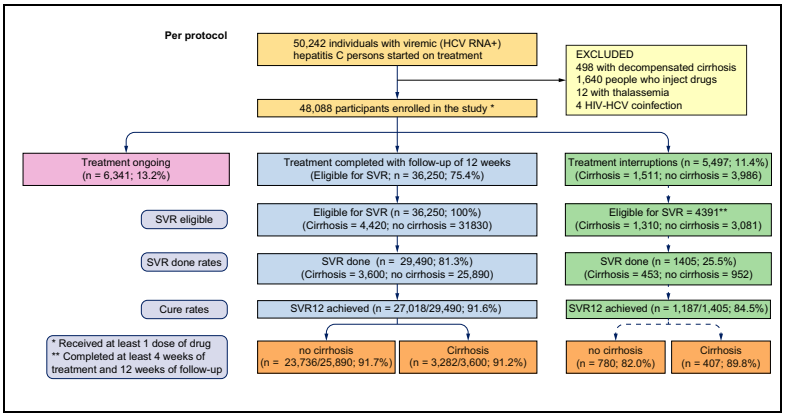
December 2019

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Decentralized care with generic direct-acting antivirals in the management of chronic hepatitis C in a public health care setting

Graphical abstract



Highlights

- The goal of the 'Punjab Model' is HCV Elimination by 2030, using primary care providers and remote treatment monitoring.
- We enrolled 48,088 people (14.8% with compensated cirrhosis; 69.9% with genotype 3).
- SVR12 was achieved in 91.6%, 67.6% and 91.2%, per protocol, intention-to-treat (ITT) and a modified ITT, respectively.
- Decentralized care of hepatitis C with direct-acting antiviral - regimens is safe and effective, regardless of genotype or presence of cirrhosis.

Authors

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Lay summary

We assessed the safety and efficacy of public health care using no-cost all-oral generic direct-acting antiviral drugs against hepatitis C in the state of Punjab, India. The goal is elimination of chronic hepatitis C (CHC) by 2030 and involves primary care providers at 25 sites in the state. We enrolled 48,088 individuals (63.8% male; mean age 42.1 years; 80.5% rural; 14.8% compensated cirrhotic; 69.9% genotype 3) between 18th June 2016 to 31st July 2018. Cure was achieved in 91.6% of patients, demonstrating that decentralized care of CHC with generic all-oral regimens is safe and effective.

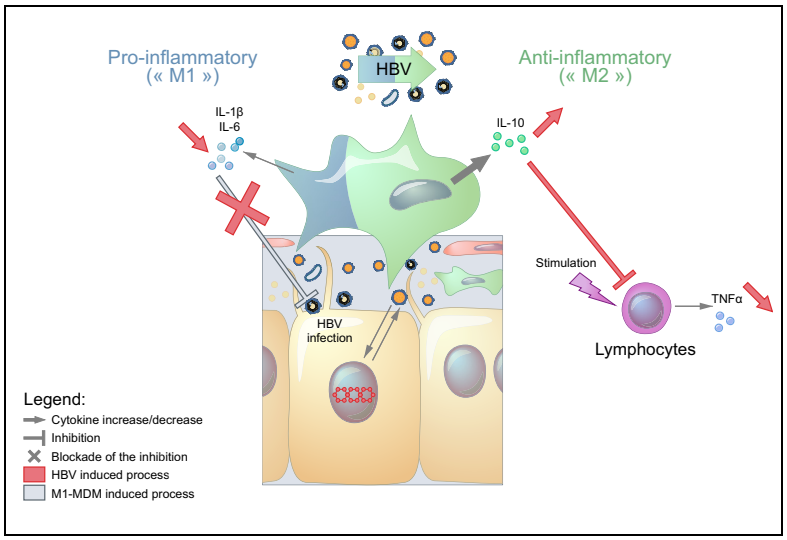
https://doi.org/10.1016/j.jhep.2019.07.006

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Hepatitis B virus-induced modulation of liver macrophage function promotes hepatocyte infection

Graphical abstract



Highlights

- Hepatitis B virus proteins are observed in liver macrophages from patients.
- Hepatitis B virus impairs pro-inflammatory macrophage secretion.
- Hepatitis B virus increases anti-inflammatory macrophage secretion.
- Impairment of pro-inflammatory secretions favours the establishment of hepatitis B virus infection.
- Increase of IL-10 secretion further impairs lymphocyte activation.

Authors

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Lay summary

Hepatitis B virus modulates liver macrophage function in order to favour the establishment and likely maintenance of infection. It impairs the production of the antiviral cytokine IL-1β, while promoting that of IL-10 in the microenvironment. This phenotype can be recapitulated in naive liver macrophages or monocyte-derived-macrophages *ex vivo* by short exposure to the virus or cells replicating the virus, thus suggesting an "easy to implement" mechanism of inhibition.

https://doi.org/10.1016/j.jhep.2019.06.032

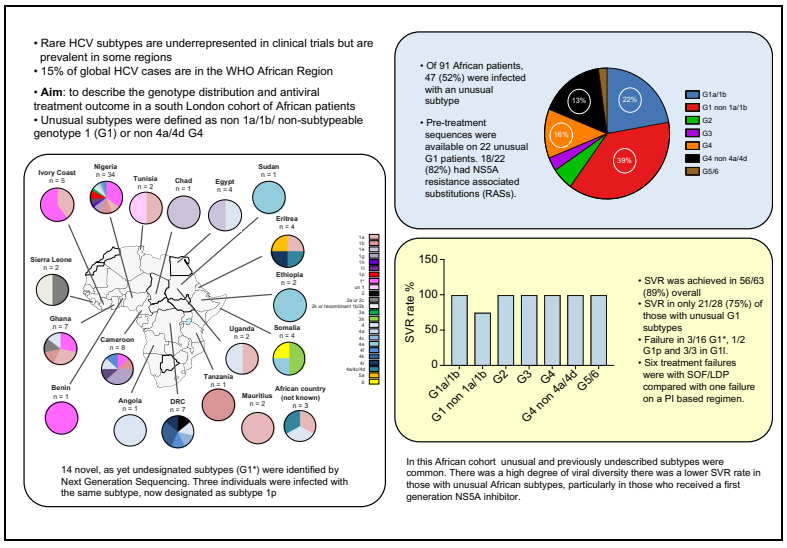
 J. Hepatol. 2019, 71, 1086–1098

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Suboptimal SVR rates in African patients with atypical genotype 1 subtypes: Implications for global elimination of hepatitis C

Graphical abstract



Highlights

- Unusual genotypes (G1 non 1a/1b or G4 non 4a/4d) were common in African patients.
- 11 previously unclassified HCV subtypes were represented including novel G1p.
- Patients with unusual G1 subtypes had a lower SVR rate than any other genotype.
- Failures were driven by patients treated with a first generation NS5A inhibitor.
- The majority of unusual G1 subtypes had baseline NS5A resistance mutations.

Authors

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Lay summary

Direct-acting antiviral medications are able to cure hepatitis C in the majority of patients. The most common genotype of hepatitis C in Europe and the United States is genotype 1a or 1b and most clinical trials focused on these genotypes. We report that in a group of African patients, most of them had unusual (non-1a/1b) genotype 1 subtypes, and that the cure rate in these unusual genotypes was lower than in genotypes 1a and 1b.

https://doi.org/10.1016/j.jhep.2019.07.025

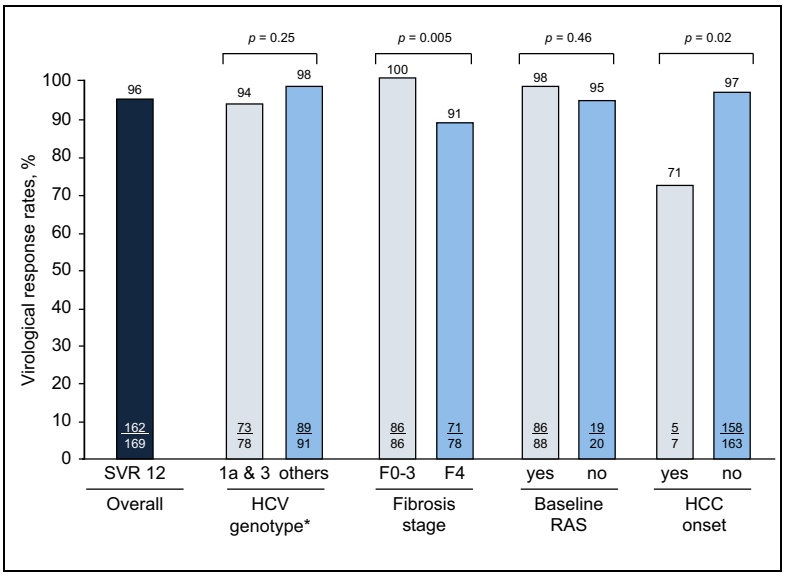
 J. Hepatol. 2019, 71, 1099–1105

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Real-life effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir in hepatitis C patients with previous DAA failure

Graphical abstract



Highlights

- SOF/VEL/VOX demonstrated excellent effectiveness in patients with HCV and previous DAA failure in a real-life study.
- Cirrhosis ($p = 0.005$) and hepatocellular carcinoma onset ($p = 0.02$) were the only features associated with treatment failure.
- Treatment failures (4%) occurred in patients with cirrhosis, with genotypes HCV-1a and 3 the most represented.

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Lay summary

This is the largest European real-life study evaluating effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) in a large cohort of consecutive patients with hepatitis C virus infection and a prior direct-acting antiviral failure, who were treated within the NAVIGATORE Lombardia and Veneto Networks, in Italy. This study demonstrated excellent effectiveness (98% and 96% sustained virological response rates at week 4 and 12, respectively) and an optimal safety profile of SOF/VEL/VOX. Cirrhosis and hepatocellular carcinoma onset were the only features associated with treatment failure.

https://doi.org/10.1016/j.jhep.2019.07.020

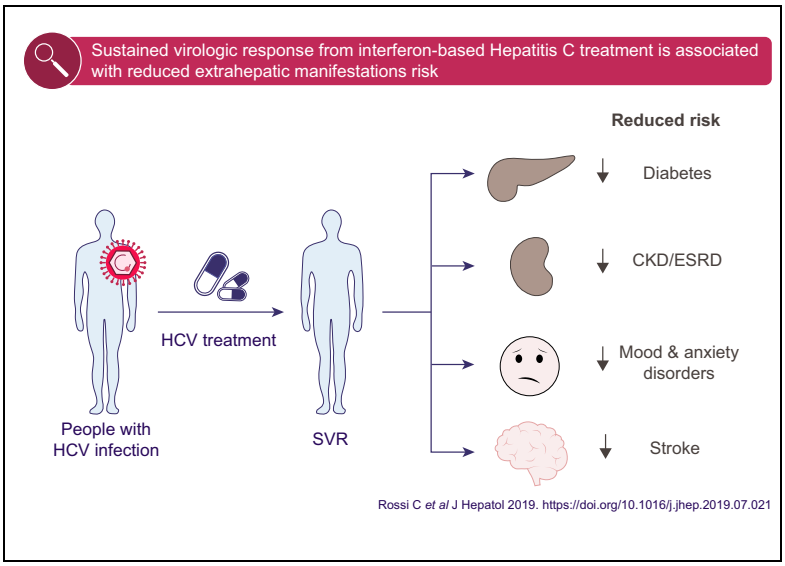
 J. Hepatol. 2019, 71, 1106–1115

Research Article
Viral Hepatitis

JOURNAL
OF HEPATOLOGY

Sustained virological response from interferon-based hepatitis C regimens is associated with reduced risk of extrahepatic manifestations

Graphical abstract



Highlights

- Chronic HCV is associated with many extrahepatic manifestations (EHMs).
- Generalizable population-level estimates of the impact of cure on EHMs are lacking.
- SVR was associated with a significant reduction in the risk of several EHMs.
- Reduction in incidence ranged from 18% (anxiety disorders) to 47% (kidney disease).

Authors

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Lay summary

We estimated the rates of chronic comorbidities other than liver disease between those who were cured and those who failed treatment for hepatitis C virus (HCV) infection. Our findings showed that the rates of these non-liver diseases were largely reduced for those who were cured with interferon-based treatments. Early HCV treatments could provide many benefits in the prevention of various HCV complications beyond liver disease.

https://doi.org/10.1016/j.jhep.2019.07.021

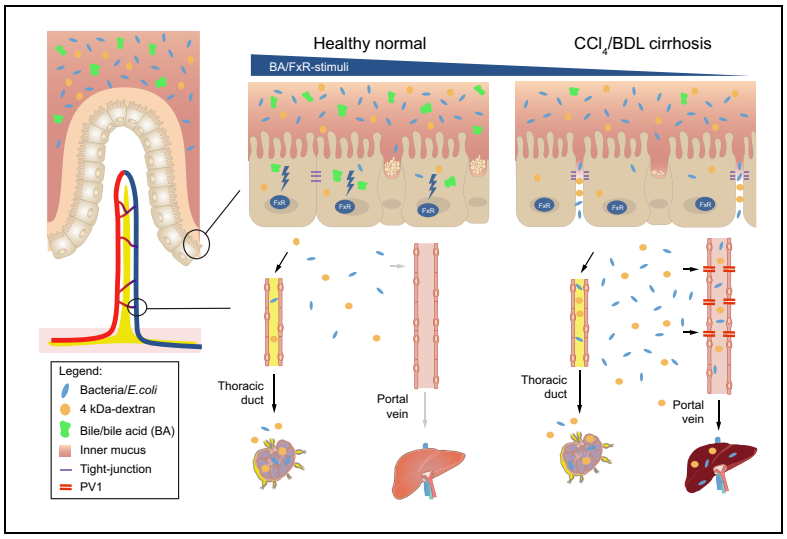
 J. Hepatol. 2019, 71, 1116–1125

Research Article
Cirrhosis

JOURNAL
OF HEPATOLOGY

FXR modulates the gut-vascular barrier by regulating the entry sites for bacterial translocation in experimental cirrhosis

Graphical abstract



Highlights

- For intestinal bacteria to enter the systemic circulation they must cross the mucus, epithelial and gut-vascular barrier.
- Cirrhosis, but not portal hypertension *per se*, grossly impairs the endothelial and muco-epithelial barriers.
- This promotes pathological bacterial translocation via the portal-venous circulation.
- Both barriers appear to be FXR-modulated, as FXR-agonists reduce portal-venous bacterial translocation.

Authors

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Lay summary

For intestinal bacteria to enter the systemic circulation, they must cross the mucus and epithelial layer, as well as the gut-vascular barrier. Cirrhosis disrupts all 3 of these barriers, giving bacteria access to the portal-venous circulation and thus, the gut-liver axis. Diminished luminal bile acid availability, cirrhosis and the associated reduction in farnesoid x receptor (FXR) signaling seem, at least partly, to mediate these changes, as FXR-agonists reduce bacterial translocation via the portal-venous route to the liver in cirrhosis.

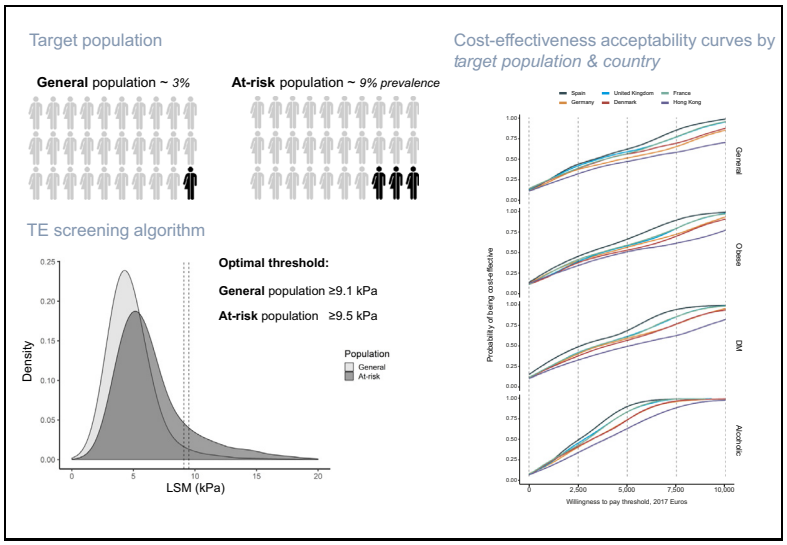
https://doi.org/10.1016/j.jhep.2019.06.017

Research Article
Cirrhosis

JOURNAL
OF HEPATOLOGY

Transient elastography for screening of liver fibrosis: Cost-effectiveness analysis from six prospective cohorts in Europe and Asia

Graphical abstract



Highlights

- Optimal liver stiffness thresholds for community-based screening of at-risk patients are 9.1–9.5 kPa for fibrosis (stages ≥F2).
- Transient elastography is a cost-effective intervention for identifying patients with liver fibrosis in primary care.
- Between 2,500 to 6,500 PPP-adjusted euros are needed to gain an extra year of life, adjusted for quality of life.
- The survival effect of screening is most pronounced for the identification of significant (≥F2) fibrosis.

Authors

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Lay summary

The lack of optimized public health screening strategies for the detection of liver fibrosis in adults without known liver disease presents a major healthcare challenge. Analyses from 6 independent international cohorts, with transient elastography measurements, show that a community-based risk-stratification strategy for alcohol-related and non-alcoholic fatty liver diseases is cost-effective and potentially cost saving for our healthcare systems, as it leads to earlier identification of patients.

https://doi.org/10.1016/j.jhep.2019.08.019

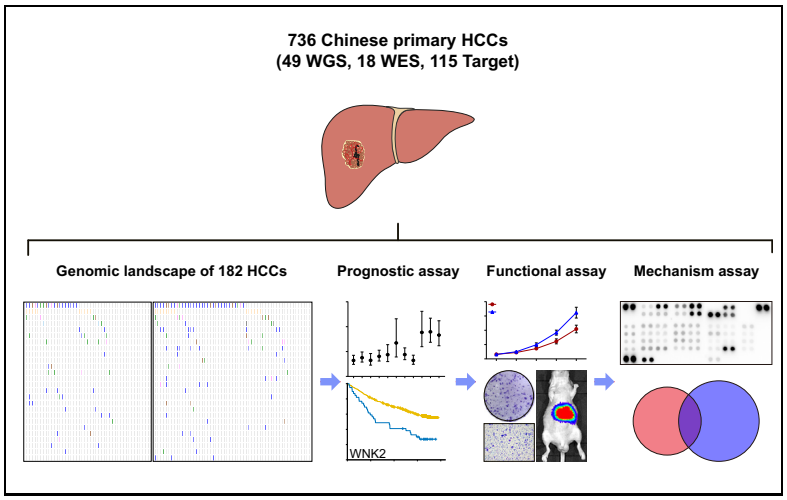
 J. Hepatol. 2019, 71, 1141–1151

Research Article
Cancer

JOURNAL
OF HEPATOLOGY

Genomic sequencing identifies WNK2 as a driver in hepatocellular carcinoma and a risk factor for early recurrence

Graphical abstract



Highlights

- 182 Chinese hepatocellular carcinomas were sequenced.
- *WNK2*, *RUNX1T1*, *CTNNB1*, *TSC1*, and *TP53* somatic mutations correlated with early tumor recurrence after curative resection.
- WNK2 displayed somatic mutation, copy number loss, and downregulated expression in HCC.
- WNK2 deficiency leads to ERK1/2 signalling activation, TAM infiltration, and tumor growth and metastasis.

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Lay summary

We applied next-generation sequencing and conducted an in-depth genomic analysis of hepatocellular carcinomas from a Chinese patient cohort. The results delineate the genomic events that characterize hepatocellular carcinomas in Chinese patients and identify *WNK2* as a driver associated with early tumor recurrence after curative resection.

https://doi.org/10.1016/j.jhep.2019.07.014

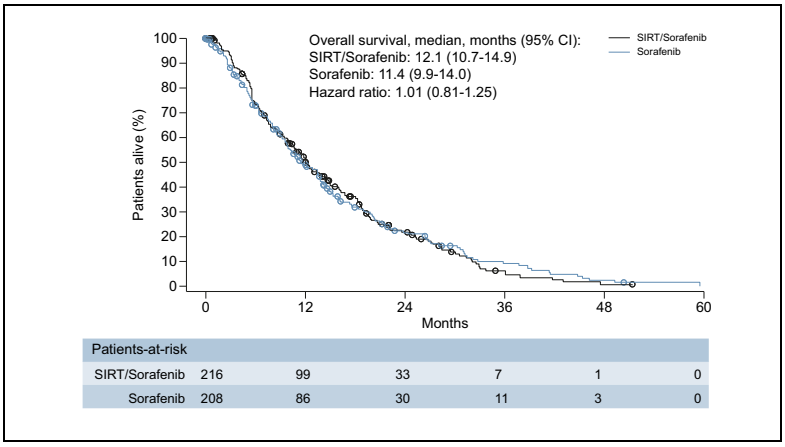
 J. Hepatol. 2019, 71, 1152–1163

Research Article
Cancer

JOURNAL
OF HEPATOLOGY

Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma

Graphical abstract



Highlights

- Sorafenib given orally is the recommended treatment for patients with advanced hepatocellular carcinoma.
- Addition of selective internal radiation therapy did not significantly improve overall survival compared to sorafenib alone.
- Subgroup analyses provided results that will guide future clinical trial designs for this combination therapy.

Authors

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Lay summary

Sorafenib given orally is the recommended treatment for patients with advanced hepatocellular carcinoma (HCC). In selective internal radiation therapy (SIRT), also known as radioembolisation, microscopic, radioactive resin or glass spheres are introduced into the blood vessels that feed the tumours in the liver. This study found that the addition of SIRT with ^{90}yttrium-loaded resin microspheres to sorafenib treatment in people with advanced HCC did not significantly improve overall survival compared with sorafenib treatment alone. However, the results give an indication of how future studies using this combination therapy in people with advanced HCC could be designed.

https://doi.org/10.1016/j.jhep.2019.08.006

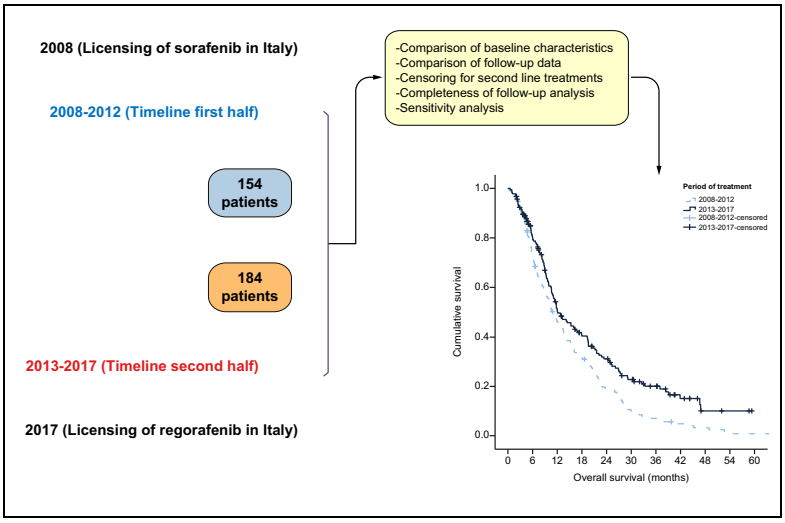
 J. Hepatol. 2019, 71, 1164–1174

Research Article
Cancer

JOURNAL
OF HEPATOLOGY

Management of adverse events with tailored sorafenib dosing prolongs survival of hepatocellular carcinoma patients

Graphical abstract



Highlights

- Management of sorafenib-related adverse events has changed over time.
- A tailored approach with more temporary dose reductions is now more frequent.
- Median treatment duration has increased overtime (5.8 *vs.* 4.1months).
- More importantly, overall survival has also increased (12.0 *vs.* 11.0months).
- Increasing survival impacts on the design of trials using sorafenib as comparator.

Authors

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Lay summary

Sorafenib has been the standard frontline systemic treatment for hepatocellular carcinoma for over a decade. Its tolerability is limited by different adverse events, which might lead to its permanent discontinuation in a sizeable proportion of patients. After a careful analysis of potential confounders, we demonstrated that the physicians experience in managing adverse events related to sorafenib has improved over time, with longer treatment periods and less permanent discontinuation for toxicities. More importantly, these improvements also translated into longer patient survival. Our results have relevant repercussions in clinical practice and in the design of future clinical trials.

https://doi.org/10.1016/j.jhep.2019.08.015

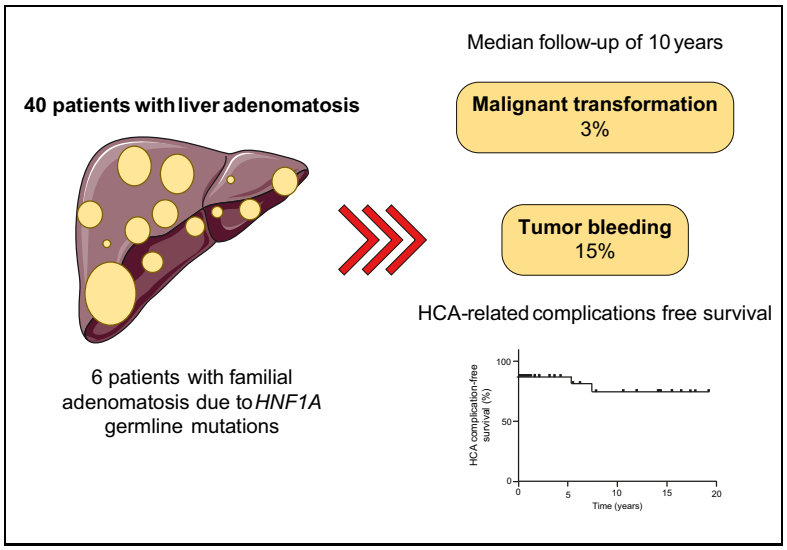
 J. Hepatol. 2019, 71, 1175–1183

Research Article
Cancer

JOURNAL
OF HEPATOLOGY

Natural history of liver adenomatosis: A long-term observational study

Graphical abstract



Highlights

- Liver adenomatosis is a rare and heterogeneous disease.
- If all adenomas are steatotic, a germline *HNF1A* mutation should be searched for.
- Risks are malignant transformation (3%) and tumor bleeding (15%, mostly inaugural).
- In familial steatotic liver adenomatosis, bleeding risk exists even in small adenomas.
- Patients with liver adenomatosis should have a specific follow-up annually, with MRI and biological tests.

Authors

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Lay summary

Liver adenomatosis is a rare disease characterized by the presence of 10 or more hepatocellular adenomas that may rarely be of genetic origin. Patients with liver adenomatosis have multiple adenomas of different subtypes, with a risk of bleeding and malignant transformation that justify a specific management and follow-up.

https://doi.org/10.1016/j.jhep.2019.08.004

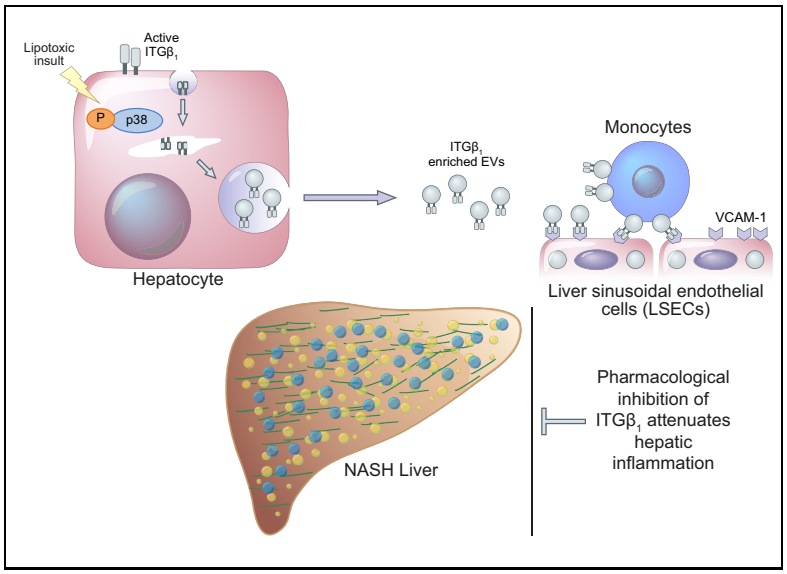
 J. Hepatol. 2019, 71, 1184–1192

Research Article
Molecular and Cell Biology

JOURNAL
OF HEPATOLOGY

Integrin β_1-enriched extracellular vesicles mediate monocyte adhesion and promote liver inflammation in murine NASH

Graphical abstract



Highlights

- Hepatocytes under lipotoxic stress release active ITGβ_1-enriched EVs.
- Lipotoxic hepatocyte-derived EVs enhance monocyte adhesion to liver sinusoidal endothelial cells mainly via their ITGβ_1 cargo.
- ITGβ_1 neutralizing antibody reduces proinflammatory monocyte hepatic infiltration in murine NASH.
- Blocking ITGβ_1 attenuates liver inflammation, injury and fibrosis in murine NASH.

Authors

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Lay summary

Herein, we report that a cell adhesion molecule termed integrin β_1 (ITGβ_1) plays a key role in the progression of non-alcoholic steatohepatitis (NASH). ITGβ_1 is released from hepatocytes under lipotoxic stress as a cargo of extracellular vesicles, and mediates monocyte adhesion to liver sinusoidal endothelial cells, which is an essential step in hepatic inflammation. In a mouse model of NASH, blocking ITGβ_1 reduces liver inflammation, injury and fibrosis. Hence, ITGβ_1 inhibition may serve as a new therapeutic strategy for NASH.

https://doi.org/10.1016/j.jhep.2019.07.019

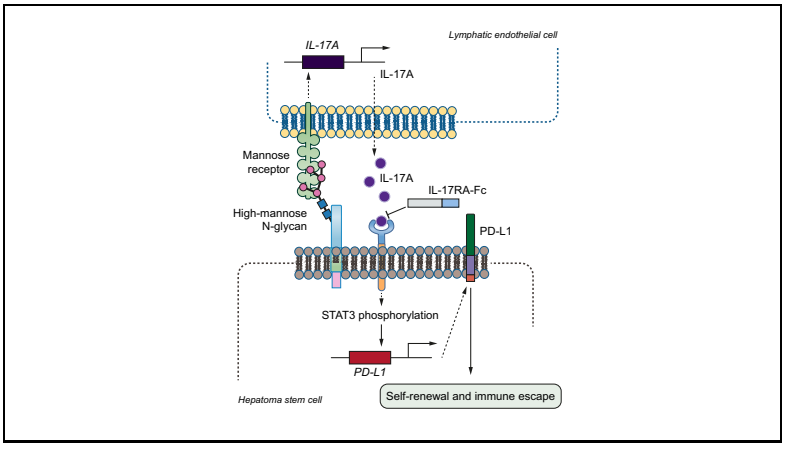
 J. Hepatol. 2019, 71, 1193–1205

Research Article
Molecular and Cell Biology

JOURNAL
OF HEPATOLOGY

IL-17A secreted from lymphatic endothelial cells promotes tumorigenesis by upregulation of PD-L1 in hepatoma stem cells

Graphical abstract



Highlights

- Hepatoma stem cells preferentially interact with lymphatic endothelial cells.
- Interaction of hepatoma stem cells with lymphatic endothelial cells upregulates IL-17A.
- IL-17A promotes hepatoma stem cell self-renewal and immune escape.
- IL-17A is highly expressed in hepatoma.

Authors

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Lay summary

The microenvironment is crucial for the self-renewal and development of hepatoma stem cells, which lead to the development of liver cancer. Lymphatic endothelial cells are an important component of this niche microenvironment, helping hepatoma stem cells to self-renew and escape immune attack, by upregulating IL-17A signaling. Thus, targeting IL-17A signaling is a potential strategy for the treatment of hepatoma.

https://doi.org/10.1016/j.jhep.2019.08.034

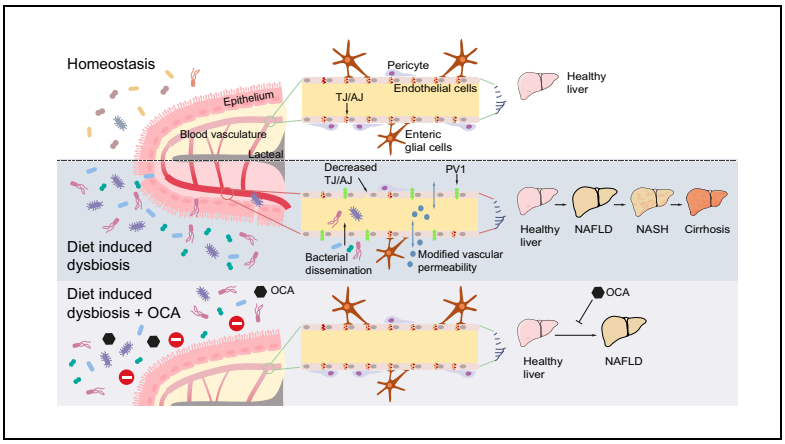
 J. Hepatol. 2019, 71, 1206–1215

Research Article
Genetic and Metabolic Diseases

JOURNAL
OF HEPATOLOGY

Microbiota-driven gut vascular barrier disruption is a prerequisite for non-alcoholic steatohepatitis development

Graphical abstract



Highlights

- During diet-induced dysbiosis the gut vascular barrier is disrupted.
- Gut vascular barrier disruption is responsible for the translocation of bacteria or bacterial products systemically.
- Inhibiting gut vascular barrier disruption prevents the development of non-alcoholic steatohepatitis.
- Obeticholic acid can control gut vascular barrier disruption both in a preventive and therapeutic way.

Authors

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Lay summary

The incidence of fatty liver disease is reaching epidemic levels in the USA, with more than 30% of adults having NAFLD (non-alcoholic fatty liver disease), which can progress to more severe non-alcoholic steatohepatitis (NASH). Herein, we show that disruption of the intestinal epithelial barrier and gut vascular barrier are early events in the development of NASH. We show that the drug obeticholic acid protects against barrier disruption and thereby prevents the development of NASH, providing further evidence for its use in the prevention or treatment of NASH.

https://doi.org/10.1016/j.jhep.2019.08.005

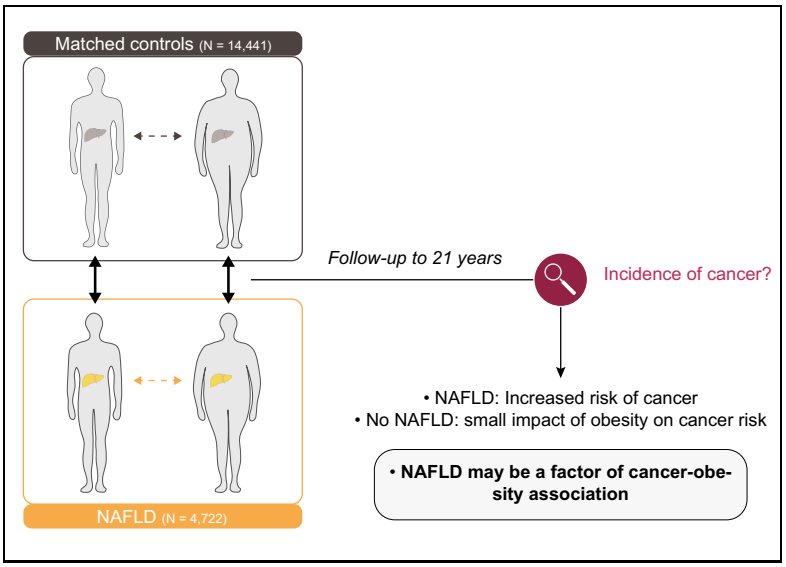
 J. Hepatol. 2019, 71, 1216–1228

Research Article
Genetic and Metabolic Diseases

JOURNAL
OF HEPATOLOGY

The risk of incident extrahepatic cancers is higher in non-alcoholic fatty liver disease than obesity – A longitudinal cohort study

Graphical abstract



Highlights

- NAFLD is associated with a nearly 2-fold increase in the overall risk of incident cancers.
- The highest risk was noted in liver, uterine, stomach, pancreas and colon cancers.
- Obesity in the absence of NAFLD had minimal impact on malignancy risk.

Authors

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Lay summary

We studied the incidence of malignancies in a community cohort of adults with non-alcoholic fatty liver disease (NAFLD) in reference to age- and sex-matched adults without NAFLD. After 21 years of longitudinal follow-up, NAFLD was associated with a nearly 2-fold increase in the risk of developing cancers, predominantly of the liver, gastrointestinal tract and uterus. The association with increased cancer risk was stronger in NAFLD than obesity.

https://doi.org/10.1016/j.jhep.2019.08.018

 J. Hepatol. 2019, 71, 1229–1236