Welcome to issue 26 of Hepatitis Research Review.

Researchers from Hong Kong report finding significantly low levels of vitamin D among untreated patients with chronic hepatitis B virus (HBV) infection. Low baseline vitamin D level was associated with lower baseline ALT level and a lower likelihood of ALT normalisation after 48 weeks of treatment, note the researchers. They add that further study is needed to determine whether a low vitamin D level contributes to unsuccessful immune clearance and active hepatitis.

Two studies report promising data with statins, which were associated with a risk reduction in hepatocellular carcinoma in a hospital-based population of HBV patients in one study and a reduced risk of cirrhosis development in patients with hepatitis C virus (HCV) infection in the other. Both studies call for further clinical research.

I hope you enjoy the selection in this issue and I welcome your comments and feedback.

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Apolipoprotein E and protection against hepatitis E viral infection in American non-Hispanic blacks

Authors: Zhang L et al.

Summary: These researchers examined variations in the genetic makeup of 3 major racial/ethnic populations in the USA who are potentially at increased risk for hepatitis E viral (HEV) infection. The analysis included data from 2434 non-Hispanic whites, 1919 non-Hispanic blacks, and 1919 Mexican Americans who participated in the Third National Health and Nutrition Examination Survey, 1991–1994. The researchers assessed strength of associations between antibody to HEV (anti-HEV) immunoglobulin G (IgG) and host genetic factors. They studied 497 single-nucleotide polymorphisms (SNPs) across 190 genes (particularly those associated with lipid metabolism). Non-Hispanic blacks had the lowest seroprevalence of anti-HEV IgG (15.3%) compared with non-Hispanic whites (22.3%) and Mexican Americans (21.8%, p<0.01). Non-Hispanic blacks were the only population to have an association between anti-HEV seropositivity and functional ε3 and ε4 alleles of the apolipoprotein E (APOE) gene, encoding the APOE protein that mediates lipoprotein metabolism. Seropositivity was significantly lower in participants carrying APOE ε4 (odds ratio[OR] 0.5; 95% CI, 0.4 to 0.7; p=0.00004) and ε3 (OR 0.6; 95% CI, 0.4 to 0.8; p=0.001) compared to those carrying APOE ε2.

No significant associations were observed between other SNPs and anti-HEV seropositivity in non-Hispanic blacks or between any SNPs and anti-HEV seropositivity in non-Hispanic whites or Mexican Americans.

Comment: This important study extends current understanding of the epidemiology and pathogenesis of HEV infection, which, although subclinical in most cases, is still the most common cause of acute viral hepatitis worldwide, with high morbidity and mortality rates in certain subgroups, risk of progression to cirrhosis in the immunosuppressed and association with a range of extrahepatic, mainly neurological, clinical syndromes. The findings illustrate a genetic basis for the observed racial distribution of anti-HEV positivity, at least in the United States. In particular, the authors found that APOE ε3 and ε4 are protective against HEV infection in those of non-Hispanic black ethnicity, with 80% and 40%, respectively, lower likelihood of seropositivity. The mechanisms responsible for these protective effects, and possible future implications for management, remain to be determined.


Abstract

In this issue:

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- Emerging combination treatment options for HCV subgroups
- Bradycardia after amiodarone + sofosbuvir + DAA

Abbreviations used in this issue:

DAA = direct-acting antiviral; FCH = fibrosing cholestatic hepatitis; HBsAg = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HEV = hepatitis E virus; IFN = interferon; FCH = fibrosing cholestatic hepatitis; VR12 = sustained virological response at week 12.
A frequent hypofunctional IRAK2 variant is associated with reduced spontaneous hepatitis C virus clearance

Authors: Wang H et al.

Summary/Comment: The innate immune response to pathogens relies on activation of Toll-like receptors and associated down-stream signalling pathways, including kinases of the interleukin-1 receptor-associated kinase (IRAK) family. In this study, the authors found that a frequent missense variant L392V, with homozygous expression in around 15% of Caucasians, is a hypofunctional IRAK2 allele, resulting in a failure of ubiquination of tumour necrosis factor-associated factor 6 (TRAF6), impaired signalling of nuclear factor kappa light-chain-enhancer of activated B cells (NF-κB) and, ultimately, reduced cytokine production in response to hepatitis C virus (HCV) infection. The findings are important clinically as well as mechanistically, as epidemiological studies suggest that the L392V variant of IRAK2 is associated with around a 30% to 50% reduced likelihood of spontaneous clearance of HCV.


Abstract

Efficacy of sofosbuvir and daclatasvir in patients with fibrosing cholestatic hepatitis C after liver transplantation

Authors: Leroy V et al.

Summary: This analysis evaluated treatment for recurrent HCV infection after liver transplantation in 23 patients with fibrosing cholestatic hepatitis (FCH). Most of the patients had genotype 1 infections that had not responded to previous treatment; 4 patients were also co-infected with HIV. Eight patients (37%) had ascites and 15 patients (65%) had bilirubin levels >100 μmol/L; the median serum HCV RNA level was 7 log IU/mL. At a median 5 months after undergoing transplantation, patients commenced treatment with sofosbuvir plus daclatasvir (n=15) or sofosbuvir plus peginterferon plus ribavirin (n=8) for 24 weeks. The primary outcome was complete clinical response (survival without re-transplantation, bilirubin level <34 μmol/L, and no ascites or hepatic encephalopathy 36 weeks after commencing treatment). All patients survived, without re-transplantation, until week 36. Patients’ median bilirubin concentrations decreased from 122 μmol/L at baseline to a normal value at week 12 of treatment. Twenty-two patients (96%) had a complete clinical response at week 36. Despite the low rate of rapid virological response, 22 patients (96%) achieved a sustained virological response at week 12 (SVR12): 15 (100%) of the sofosbuvir+daclatasvir group and 7 (88%) of the sofosbuvir+peginterferon+ribavirin group. The only relapse of HCV infection occurred in a patient with HIV infection who received sofosbuvir plus ribavirin. There were no grade 3 or 4 adverse events related to sofosbuvir or daclatasvir and no significant drug-drug interactions.

Comment: Historically, the recurrence of HCV infection following liver transplantation in the fibrosing cholestatic form was a dreaded development, with inevitable graft loss within two years in untreated patients. Even in treated patients, efficacy prior to the direct-acting antiviral (DAA) era was limited at best, with pegylated-interferon-based therapy associated with a virological or biochemical response in only around 35%. With new all-oral DAA combinations, a message is emerging that severe fibrosing cholestatic hepatitis C following liver transplantation is successfully treatable, leading to a sustained virological response, in the majority of patients. This study adds to that experience with a cohort of 23 patients, 22 (96%) of whom experienced both SVR12 and rapid improvement in both clinical and laboratory parameters. The findings reinforce the message that fibrosing cholestatic hepatitis C post-liver transplant needs no longer be viewed as the serious threat to graft and overall survival that it was in the past.


Abstract

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Expression and functionality of Toll- and RIG-like receptors in HepaRG cells
Authors: Luangsay S et al.
Summary: This study sought to determine the innate immune functions of HepaRG cells, which currently serve as the best surrogate model for investigations into host-pathogen interactions in primary human hepatocyte (PHH) culture. Gene and expression levels of Toll-like receptors (TLR)-1 to 9 and retinoic acid-inducible gene-1 (RIG-I)-like receptors (RLR) were examined in HepaRG cells. The basal gene and protein expression profile of TLR/RLR in HepaRG cells was similar to that of PHH. Most receptors, except for TLR-7 and 8, were expressed as proteins and functionally active as shown by the induction of some innate genes, as well as by the secretion of interleukin (IL)-6 and interferon-γ-inducible protein-10 (IP-10), upon agonist stimulation. The highest levels of IL-6 and IP-10 secretion were obtained by TLR-2 and TLR-3 agonist stimulation, respectively. The highest preventive antiviral activity against hepatitis B virus (HBV) was obtained following TLR-2, TLR-4 or RIG-1/MDA-5 stimulations, which correlated with their high capacity to produce both cytokines.

Comment: HepaRG cells are bipotential liver progenitor cells that differentiate into both cholangiocyte-like and hepatocyte-like cells in culture. These cells are a suitable in vitro model for studying differentiated hepatocyte function and have been shown to be functional in terms of interferon signalling. This study found that the innate pattern recognition receptors, TLRs and RLRs, are also functional in HepaRG cells. The findings are relevant in that they demonstrate that HepaRG cells represent a suitable model to study innate immune responses to hepatotropic viruses that occur specifically within hepatocytes.

Reference: J Hepatol. 2015;63(5):1077-85
Abstract

Association of baseline vitamin D levels with clinical parameters and treatment outcomes in chronic hepatitis B
Authors: Chan HL et al.
Summary: This group of researchers in Hong Kong measured pretreatment serum vitamin D (25-hydroxyvitamin D₃; 25[OH]D₃) levels and determined their association with clinical parameters and treatment outcomes in 737 patients with chronic HBV without advanced liver disease, who were randomised to either tenofovir disoproxil fumarate (TDF) plus peginterferon (PegIFN) or TDF plus PegIFN. The highest preventive antiviral activity against hepatitis B virus (HBV) was associated with low HBV DNA, normal ALT and lower uric acid levels, hepatitis B e antigen (HBeAg)-positive status, and 58% had deficient (<20 ng/mL) vitamin D levels. Younger age, entry, 35% of the patients had insufficient (≥20 but <31 ng/mL) vitamin D levels. Similarly, vitamin D status did not significantly impact upon treatment outcomes in chronic hepatitis B with clinical parameters and treatment outcomes. In a Cox proportional hazard regression analysis, the adjusted hazard ratios were 0.33 (95% CI, 0.31 to 0.36), 0.24 (95% CI, 0.22 to 0.25), and 0.13 (95% CI, 0.12 to 0.15) for statin use of 28–83, 84–365, and >365 cDDD, respectively, relative to no statin use (<28 cDDD).

Comment: Statin use and the risk of cirrhosis development in patients with hepatitis C virus infection
Authors: Yang Y-H et al.
Summary: For this population-based cohort study, data were obtained from the Taiwan National Health Insurance Research Database concerning 226,856 patients with HCV infection, each of whom was followed from 1997 to 2010 to identify incident cases of cirrhosis. A total of 34,273 cases of cirrhosis were identified with HCV infection during the follow-up period of 2,874,031.7 person-years. The incidence rate was 445.5 cases of cirrhosis per 100,000 person-years for statin users (defined as those who used more than 28 cumulative defined daily doses [cDDD]), and 1311.2 cirrhosis cases per 100,000 person-years for non-users. A dose-response relationship between statin use and cirrhosis risk was observed. In a Cox proportional hazard regression analysis, the adjusted hazard ratios were 0.33 (95% CI, 0.31 to 0.36), 0.24 (95% CI, 0.22 to 0.25), and 0.13 (95% CI, 0.12 to 0.15) for statin use of 28–83, 84–365, and >365 cDDD, respectively, relative to no statin use (<28 cDDD).

Comment: The long-term benefits of nucleos(t)ide analogs in compensated HBV cirrhotic patients with no or small esophageal varices: A 12-year prospective cohort study
Authors: Lamberto P et al.
Summary: Data are reported from 107 patients with HBeAg-negative HBV infection and compensated cirrhosis (93% Child-Pugh A) who underwent 414 upper gastrointestinal endoscopies during a median 12 years of nucleos(t)ide analogue use. Patients who initially started on lamivudine and then developed resistance were rescued by early administration of tenofovir, or were switched to tenofovir. Twenty-seven patients had baseline F1 esophageal varices, which regressed in 18, remained unchanged in 8 and progressed in 1 patient; the 12-year cumulative incidence of esophageal varices regression was 83%. De novo F1/F2 esophageal varices developed in 6/80 patients with a 12-year cumulative incidence of 10%. Six of 7 patients with de novo varices or progression of pre-existing varices had either a clinical breakthrough due to lamivudine resistance and/or developed a HCC. No bleedings from ruptured esophageal varices occurred, 12 patients died (9 HCC) and 15 were transplanted (13 HCC); the 12-year cumulative incidence of HCC and overall survival was 33% and 76%, respectively.

Comment: Portal hypertension is a well-established indicator of poor outcome in patients with cirrhosis. This study was performed to assess the effects of nucleos(t)ide analogue therapy on esophageal varices in 107 patients with well-compensated cirrhosis due to chronic, HBeAg-negative HBV infection. The results are important in demonstrating that effective, long-term pharmacological suppression of HBV replication in this group is associated with both regression of pre-existing esophageal varices and only a very low risk of the de novo development of varices. The data lend further support to the benefits of achieving effective viral suppression in patients with HBV-associated cirrhosis.

Reference: J Hepatol. 2015;63(5):1118-25
Abstract

Statin and the risk of hepatocellular carcinoma and death in a hospital-based hepatitis B-infected population: A propensity score landmark analysis
Authors: Hsiang JC et al.
Summary: The Hospital Authority database in Hong Kong was used to examine the effect of statin therapy on hepatocellular carcinoma (HCC) and death in this hospital-based population study of HBV patients. A total of 73,409 patients with a crude HCC incidence of 1.75 per 100 patient-years were entered into the 2-year landmark analysis. After landmark analysis and propensity score weighting of baseline covariates, statin users had a 52% risk reduction in HCC (weighted sub-hazard ratio [SHR] 0.48; 95% CI, 0.38 to 0.57) compared with non-users. There was no decrease in risk of death in statin users (weighted HR 0.72 to 1.11; p=0.386). In subgroup analysis, concurrent statin and nucleos(t)ide analogue use was associated with a 59% risk reduction in HCC (weighted SHR 0.41; 0.19-0.89; p=0.023) compared to nucleos(t)ide analogue alone use.

Comment: Statin use was found in a recent population study to reduce risk of HCC in patients with chronic HBV infection by up to 67%. This territory-wide, retrospective cohort study, performed in Hong Kong and including a hospital-based cohort of over 73,000 patients with chronic HBV and using a 2-year landmark analysis method to adjust for confounders and biases, investigated the effect of statin use for the primary chemoprevention of HCC, including in a subgroup concomitantly managed with a nucleos(t)ide analogue. The authors found a 52% risk reduction for HCC with statin use, while concurrent use of a statin and nucleos(t)ide antiviral therapy was associated with a 59% risk reduction compared to treatment with a nucleos(t)ide analogue alone. This additive risk reduction with combined statin and nucleos(t)ide analogue therapy, in particular, warrants further assessment in prospective randomised trials.

Reference: J Hepatol. 2015;63(5):1119-7
Abstract
Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alfa in patients with hepatitis C virus genotype 3 infection and treatment-experienced patients with cirrhosis and hepatitis C virus genotype 2 infection

Authors: Foster GR et al.

Summary: This open-label phase 3 trial enrolled 48 treatment-experienced patients with cirrhosis and HCV genotype 2 infection and 279 treatment-naïve or 265 treatment-experienced patients with HCV genotype 3 infection. Overall, 219 patients had compensated cirrhosis. Study participants were randomly assigned to treatment with sofosbuvir plus ribavirin for 16 weeks (n=196) or 24 weeks (n=199), or sofosbuvir plus PegIFN-α and ribavirin for 12 weeks (n=197). Among patients with genotype 2 HCV infection, SVR12 rates were 87% and 100%, for those receiving 16 and 24 weeks of sofosbuvir plus ribavirin, respectively, and 94% for those receiving sofosbuvir plus PegIFN-α and ribavirin for 12 weeks. Among patients with genotype 3 HCV infection, SVR12 rates were 71% and 84% in those receiving 16 and 24 weeks of sofosbuvir plus ribavirin, respectively, and 93% in those receiving sofosbuvir plus PegIFN-α and ribavirin. On-treatment virological failure occurred in 3 patients with genotype 3a HCV given sofosbuvir plus ribavirin for 24 weeks. The most common adverse events were fatigue, headache, insomnia, and nausea. Overall, 1% of patients discontinued treatment due to adverse events.

Comment: This phase III, open-label, multicentre study shows superior SVR12 in patients with genotype 3 HCV who are treated with 12 weeks of sofosbuvir + pegylated-interferon + ribavirin compared with those treated with either 16 weeks or 24 weeks of sofosbuvir + ribavirin, with this finding consistent across all subgroups. Sofosbuvir + ribavirin for 24 weeks should be viewed as a fall-back treatment option in genotype 3-infected HCV patients in whom pegylated-interferon is contraindicated or poorly tolerated. In treatment-experienced cirrhotic patients with genotype 2 HCV infection, SVR12 rates were comparably high for each of these treatment options. The findings provide further perspectives on emerging combination treatment options in particular subgroups of patients with chronic HCV infection.

Reference: Gastroenterology. 2015;149(6):1462-70

Abstract

Extreme bradycardia after first doses of sofosbuvir and daclatasvir in patients receiving amiodarone: 2 cases including a rechallenge

Authors: Renet S et al.

Summary: This paper presents the details of 2 patients receiving amiodarone who developed extreme bradycardia within 2 hours after intake of sofosbuvir and daclatasvir. The first patient had a cardiac asystole 30 min after receiving sofosbuvir and daclatasvir. Amiodarone, sofosbuvir and daclatasvir treatment were stopped; after 10 days, the cardiac evaluation was normal and the patient was discharged. The second patient was taking amiodarone and propranolol; 2 hours after receiving sofosbuvir and daclatasvir, he had an extreme sinus node dysfunction (heart rate of 27 beats/min). Amiodarone and propranolol were stopped, but the patient continued receiving sofosbuvir and daclatasvir for 3 days and sinus bradycardia was recorded each day. 2 hours after intake of these drugs. After stopping sofosbuvir and daclatasvir, the patient had no bradycardia episodes. On day 13, 2 hours after intake of sofosbuvir and daclatasvir, bradycardia was recorded. However, no bradycardia occurred following a rechallenge 8 weeks after the patient stopped taking amiodarone.

Comment: A safety announcement issued by the US Food and Drug Administration (FDA) in March 2015, based on a total of nine postmarketing reports, warned of risk of serious bradycardia when the class III antiarrythmic drug, amiodarone, is used in combination with sofosbuvir along with another direct-acting antiviral agent for the treatment of chronic HCV infection. This series of two cases, presumably included in those nine reports mentioned by the FDA, is therefore a timely reminder of the potential serious risk imposed when these drugs are used together. The responsible mechanism is as yet uncertain.

Reference: Gastroenterology. 2015;149(6):1378-80

Abstract