
**BACKGROUND:** The correctional population bears a heavy burden of hepatitis C virus (HCV) infection necessitating expansion of HCV testing and treatment opportunities. Rapid HCV testing provides point-of-care antibody results and may be ideal for correctional facilities, particularly jails, where persons are often incarcerated for short periods of time, yet feasibility has not been established.

**METHODS:** We conducted a pilot study of a rapid HCV testing algorithm among short-term inmates with unknown HCV status. Participants completed a questionnaire, viewed an informational video and underwent rapid HCV testing and confirmatory testing, when indicated. Persons with chronic infection were referred to community care after release. Baseline characteristics, risk behaviors, test results and linkage were examined by descriptive analyses.

**RESULTS:** Two hundred and fifty-two inmates were enrolled and 249 completed all study activities. Twenty-five participants (10%) had reactive rapid tests and 23 (92%) completed confirmatory testing. 15/23 (65%) had detectable HCV RNA, but only 4 linked to care after release. Persons with reactive HCV tests were more likely to be White (P = 0.01) and to have ever injected (P < 0.0001) and/or recently injected (P < 0.0001) drugs.

**CONCLUSIONS:** Rapid HCV testing within jails is feasible, identifies previously unrecognized cases of HCV infection, and implementation should be considered. Low rates of linkage to care after release remain a barrier to care.


**BACKGROUND & AIMS:** Osteopontin (OPN) is a matricellular protein that upregulates during pathogenesis of hepatic fibrosis. The present study was aimed to evaluate whether serum OPN could be used as a biomarker to assess the degree of hepatic fibrosis in patients with hepatitis C virus (HCV) infection. **METHODS:** Needle biopsy was performed on HCV patients and scored as zero fibrosis (F0), mild fibrosis (F1), moderate fibrosis (F2), severe fibrosis (F3) and liver cirrhosis (F4) based on Masson's trichrome and α-smooth muscle actin (α-SMA) staining. Serum OPN levels were measured using ELISA and correlated with the degree of...
fibrosis. Furthermore, the OPN values were correlated and evaluated with platelets count, serum hyaluronic acid (HA), and collagen type IV and subjected to receiver operating characteristic (ROC) curve analysis. **RESULTS:** Serum OPN levels were remarkably increased from F0 through F4 in a progressive manner and the differences were significant (P < 0.001) between each group. The data were highly correlated with the degree of hepatic fibrosis. The ROC curve analysis depicted that serum OPN is an independent risk factor and an excellent biomarker and a prognostic index in HCV patients. **CONCLUSIONS:** The results of the present study indicate that serum OPN levels reflect the degree of hepatic fibrosis and could be used as a biomarker to assess the stage of fibrosis in HCV patients which would help to reduce the number of liver biopsies. Furthermore, serum OPN serves as a prognostic index towards the progression of hepatic fibrosis to cirrhosis and hepatocellular carcinoma.


**BACKGROUND & AIMS:** HCV-infected patients with a history of injection drug use have low rates of initiation and completion of interferon-based therapies. This study evaluated efficacy, safety, and pharmacokinetics of a 12-week all-oral regimen of ombitasvir/paritaprevir/ritonavir and dasabuvir +ribavirin in HCV genotype 1-infected patients on stable opioid replacement therapy. **METHODS:** This was a phase 2, multicenter, open-label, single arm study in treatment-naïve or peginterferon/ribavirin-treatment experienced HCV genotype 1-infected patients on methadone or buprenorphine +/-naloxone. Patients received 12 weeks of co-formulated ombitasvir/paritaprevir/ritonavir(25mg/150mg/100mg once daily) and dasabuvir(250mg twice daily) +weight-based ribavirin. The primary efficacy endpoint was sustained virologic response 12 weeks post-treatment. **RESULTS:** Thirty-eight non-cirrhotic patients on chronic methadone(n=19) or buprenorphine(n=19) were enrolled. A total of 37 patients(97.4%) had a sustained virologic response 12 weeks post-treatment. No patient had a viral breakthrough or relapse. One patient discontinued due to serious adverse events unrelated to study drug (cerebrovascular accident and sarcoma). The most frequent adverse events were nausea, fatigue, and headache. Eight patients had on-treatment hemoglobin concentrations <10g/dL. Pharmacokinetic analyses indicated no clinically meaningful impact of methadone or buprenorphine on ombitasvir, paritaprevir, ritonavir, dasabuvir, or dasabuvir M1 metabolite exposures. No dose adjustments of methadone or buprenorphine were required. **CONCLUSIONS:** The interferon-free regimen of ombitasvir/paritaprevir/r and dasabuvir +ribavirin for 12 weeks was well-tolerated and achieved sustained virologic response in 97.4% of patients on opioid substitution therapy in this study. This all-oral regimen may provide an effective alternative to interferon-based therapies for HCV-infected patients with a history of injection drug use.

BACKGROUND: Patients with cirrhosis resulting from chronic hepatitis C virus (HCV) infection are at risk of life-threatening complications, but consistently achieve lower sustained virological response (SVR) than patients without cirrhosis, especially if treatment has previously failed. We assessed the efficacy and safety of the NS5A inhibitor ledipasvir and the nucleotide polymerase inhibitor sofosbuvir, with and without ribavirin. METHODS: In this multicentre, double-blind trial, between Oct 21, 2013, and Oct 30, 2014, we enrolled patients with HCV genotype 1 and compensated cirrhosis who had not achieved SVR after successive treatments with pegylated interferon and protease-inhibitor regimens at 20 sites in France. With a computer-generated randomisation sequence, patients were assigned in a 1:1 ratio to receive placebo matched in appearance to study drugs for 12 weeks followed by once daily combination fixed-dose tablets of 90 mg ledipasvir and 400 mg sofosbuvir plus weight-based ribavirin for 12 weeks, or ledipasvir-sofosbuvir plus placebo once daily for 24 weeks. The primary endpoint was SVR12 weeks after the end of treatment (SVR12), for which 95% CIs were calculated with the Clopper-Pearson method. This study is registered with ClinicalTrials.gov, number NCT01965535. FINDINGS: Of 172 patients screened, 155 entered randomisation, 77 were assigned to receive ledipasvir-sofosbuvir plus ribavirin and 78 ledipasvir-sofosbuvir. 114 (74%) were men, 151 (97%), were white, 98 (63%) had HCV genotype 1a, and 145 (94%) had non-CC IL28B alleles. SVR12 rates were 96% (95% CI 89–99) for patients in the ledipasvir-sofosbuvir plus ribavirin group and 97% (91–100) in the ledipasvir-sofosbuvir group. One patient discontinued treatment because of adverse events while receiving only placebo. The most frequent adverse events were asthenia and headache, pruritus, and fatigue. INTERPRETATION: Ledipasvir-sofosbuvir plus ribavirin for 12 weeks and ledipasvir-sofosbuvir plus placebo once daily for 24 weeks provided similarly high SVR12 rates in previous non-responders with HCV genotype 1 and compensated cirrhosis. The shorter regimen, when given with ribavirin, might, therefore, be useful to treat treatment-experienced patients with cirrhosis if longer-term treatment is not possible.


Treatment options for patients with hepatitis C virus (HCV) genotype 3 infection are limited, with the currently approved all-oral regimens requiring 24-week treatment and the addition of ribavirin (RBV). This phase III study (ALLY-3; ClinicalTrials.gov: NCT02032901) evaluated the 12-week regimen of daclatasvir (DCV; pangenotypic nonstructural protein [NS]5A inhibitor) plus sofosbuvir (SOF; pangenotypic NS5B inhibitor) in patients infected with genotype 3. Patients were either treatment naïve (n = 101) or treatment experienced (n = 51) and received DCV 60 mg plus SOF 400 mg once-daily for 12 weeks. Coprimary endpoints were the proportions of treatment-naïve and treatment-experienced patients achieving a sustained virological response (SVR) at post-treatment week 12 (SVR12). SVR12 rates were 90% (91 of 101) and 86% (44 of 51) in treatment-naïve and treatment-experienced patients, respectively; no virological breakthrough was observed, and ≥99% of patients had a virological response (VR) at...
the end of treatment. SVR12 rates were higher in patients without cirrhosis (96%; 105 of 109) than in those with cirrhosis (63%; 20 of 32). Five of seven patients who previously failed treatment with an SOF-containing regimen and 2 of 2 who previously failed treatment with an alisporivir-containing regimen achieved SVR12. Baseline characteristics, including gender, age, HCV-RNA levels, and interleukin-28B genotype, did not impact virological outcome. DCV plus SOF was well tolerated; there were no adverse events (AEs) leading to discontinuation and only 1 serious AE on-treatment, which was unrelated to study medications. The few treatment-emergent grade 3/4 laboratory abnormalities that were observed were transient.

CONCLUSION: A 12-week regimen of DCV plus SOF achieved SVR12 in 96% of patients with genotype 3 infection without cirrhosis and was well tolerated. Additional evaluation to optimize efficacy in genotype 3-infected patients with cirrhosis is underway. (Hepatology 2015;61:1127-1135).


**BACKGROUND AND AIMS:** The incidence of non-alcoholic fatty liver disease (NAFLD) is increasing worldwide. We evaluated serum collagen IV as a direct non-invasive marker of severe liver fibrosis in NAFLD.

**METHODS:** The study included 148 NAFLD and 187 chronic hepatitis C patients in whom histological severity of liver fibrosis was evaluated. The utility of serum collagen IV measured by immune-mediated agglutination using two types of monoclonal antibodies for distinguishing severe fibrosis (≥ stage 3 and ≥ F3) from non-to-moderate fibrosis in NAFLD or chronic hepatitis C was assessed in comparison to serum hyaluronic acid or other indirect fibrosis markers.

**RESULTS:** Multiple logistic regression analysis showed that serum collagen IV was significantly associated with severe fibrosis in NAFLD (odds ratio: 1.21, p<0.001) but not in chronic hepatitis C. For distinguishing severe fibrosis in NAFLD, collagen IV showed the largest area under the receiver-operating characteristic curve (0.827, 95%CI: 0.746-0.908) followed by FIB-4 (0.805, 95%CI: 0.728-0.890); in chronic hepatitis C, those for FIB-4 (0.813, 95%CI: 0.748-0.878) and collagen IV (0.770, 95%CI: 0.683-0.857) were the largest and smallest, respectively. To detect severe fibrosis in NAFLD, a cutoff of collagen IV > 177 exhibited 77.1% sensitivity, 84.0% specificity, 76.5% positive predictive value, and 84.0% negative predictive value. Combined with a cutoff of FIB-4 > 2.09, the negative and positive predictive values, and specificity for detecting severe fibrosis in NAFLD increased further.

**CONCLUSION:** Collagen IV is a reliable marker for distinguishing severe liver fibrosis from non-to-moderate fibrosis in NAFLD but not chronic hepatitis C.


**BACKGROUND:** Hepatitis C virus (HCV) RNA loads serve as predictors of treatment response during interferon-based therapy. We evaluated the predictive ability of HCV RNA levels at end of treatment (EOT) for sustained virologic response (SVR12) during interferon-sparing direct-acting antiviral therapies.

**METHODS:** HCV genotype 1-infected, treatment-naive patients were treated with sofosbuvir and ribavirin for 24 weeks (n = 55), sofosbuvir and ledipasvir for 12 weeks (n = 20), sofosbuvir, ledipasvir, and GS-9669 for 6 weeks (n = 20), or sofosbuvir, ledipasvir, and GS-9451 for 6 weeks (n = 19). Measurements of HCV RNA were performed...
using the Roche COBAS TaqMan HCV test and the Abbott RealTime HCV assay. Positive predictive value (PPV) and negative predictive value (NPV) of HCV RNA less than the lower limit of quantification (<LLOQ) at EOT for SVR12 were calculated. **RESULTS:** All 55 patients treated with sofosbuvir and ribavirin had HCV RNA <LLOQ at EOT by the Roche and Abbott assays, but only 38 achieved SVR12 (PPV, 69%). Among patients treated with sofosbuvir and ledipasvir with or without GS-9669 or GS-9451, 100% (59/59) had HCV RNA <LLOQ by the Roche assay and 1 relapsed (PPV, 98%). By the Abbott assay, 90% (53/59) had HCV RNA <LLOQ, of whom 1 patient relapsed (PPV, 98%). Notably, 6 patients with HCV RNA ≥LLOQ at EOT (range, 14-64 IU/mL) achieved SVR12 (NPV, 0%). Quantifiable HCV RNA (range, 15-57 IU/mL) was measured 2 weeks posttreatment in 4 individuals, and 4 weeks posttreatment in 1 patient (14 IU/mL). **CONCLUSIONS:** Contrary to past experience with interferon-containing treatments, low levels of quantifiable HCV RNA at EOT do not preclude treatment success.


**PURPOSE:** The aim of this study was to evaluate changes in ocular surface and tear function parameters in chronic hepatitis C at initial stages of hepatic fibrosis. **METHODS:** Thirty-one patients with biopsy-proven chronic hepatitis C and 31 age- and sex-matched healthy control subjects without systemic hepatitis C infection were examined with the Ocular Surface Disease Index (OSDI) questionnaire, Schirmer I, tear film break-up time, and scoring of ocular surface fluorescein and Rose Bengal staining using modified Oxford and van Bijsterveld scoring systems, respectively. **RESULTS:** All ocular surface parameters, except OSDI and corneal staining scores, were significantly worse in hepatitis C group. The control group had greater OSDI scores than the hepatitis C group, but there was no statistically important difference. In subgroup analysis, progression of hepatic fibrosis was found to be correlated strongly with decreased Schirmer test I, increased OSDI, lid parallel conjunctival folds, conjunctival, and corneal staining scores. **CONCLUSION:** Patients with chronic hepatitis C were more likely to exhibit severe ocular surface damage and signs of dry eye.

**BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES**

**Hepatitis C virus core protein induces epithelial-mesenchymal transition in human hepatocytes by upregulating E12/E47 levels.** Tiwari I1, Yoon MH2, Park BJ2, Jang KL3. Cancer Lett. 2015 Jun 28;362(1):131-8. doi: 10.1016/j.canlet.2015.03.032. Epub 2015 Mar 27. Downregulation of E-cadherin is a hallmark of epithelial-mesenchymal transition (EMT), an essential component of cancer progression to more aggressive phenotypes characterized by tumor dedifferentiation, infiltration, and metastasis. However, the underlying mechanism for E-cadherin downregulation in hepatitis C virus (HCV)-associated hepatocellular carcinoma (HCC) is still unclear. In this study, we found that ectopic expression of HCV core protein or infection with HCV in human hepatocytes upregulated the levels of the transcriptional repressors, E12 and E47, resulting in inactivation of the E-cadherin promoter, containing E-box motifs, and subsequent repression of its expression. E12/E47 knock-down almost completely abolished the potential of HCV core protein to repress E-cadherin expression. HCV core protein inhibited ubiquitin-dependent proteasomal degradation of E12/E47 without affecting their expression at
the transcriptional level. E12/E47 upregulation ultimately led to EMT in human hepatocytes, as demonstrated by morphological changes, altered expression levels of EMT markers, including E-cadherin, plakoglobin, and fibronectin, and increased capacity for cell detachment and migration. In conclusion, HCV core protein represses E-cadherin expression by upregulating E12/E47 levels to induce EMT in HCV-associated HCC.

**Hepatitis C virus structural proteins can exacerbate or ameliorate acetaminophen-induced liver injury in mice.** Ramachandran A1, Lebofsky M, Yan HM, Weinman SA, Jaeschke H. Arch Toxicol. 2015 May;89(5):773-83. doi: 10.1007/s00204-015-1498-5. Epub 2015 Mar 6. Chronic hepatitis C virus (HCV) infection predisposes patients to develop liver failure after acetaminophen (APAP) overdose. Mechanisms involved in this were explored using transgenic mice expressing the HCV structural proteins core, E1 and E2. Treatment of C57BL/6J mice with 200 mg/kg body weight APAP resulted in significant liver injury at 6 h as indicated by elevated ALT levels, focal centrilobular necrosis and nuclear DNA fragmentation. HCV transgenic mice showed a variable response, with approximately half the animals showing exacerbation of all parameters of liver injury, while the other half was protected. HCV transgenic mice with higher liver injury had lower liver glutathione levels, elevated mitochondrial oxidative stress and enhanced release of apoptosis-inducing factor (AIF) from the mitochondria. This was accompanied by induction of a higher ER stress response and induction of autophagy. Transgenic animals showing protection against liver injury had a robust recovery of liver glutathione content at 6 h when compared to wild-type animals, accompanied by reduction in mitochondrial oxidative stress and AIF release. This was accompanied by an elevation in glutathione S-transferase mRNA levels and activity, which suggests that an efficient clearance of the reactive intermediate may contribute to the protection against APAP hepatotoxicity in these mice. These results demonstrate that while HCV infection could exacerbate APAP-induced liver injury due to induction and amplification of mitochondrial oxidant stress, it could also protect against injury by activation of APAP scavenging mechanisms.

**HCV Induces the Expression of Rubicon and UVRAG to Temporally Regulate the Maturation of Autophagosomes and Viral Replication.** Wang L1, Tian Y1, Ou JH1. PLoS Pathog. 2015 Mar 25;11(3):e1004764. doi: 10.1371/journal.ppat.1004764. eCollection 2015. Hepatitis C virus (HCV) induces autophagy to enhance its replication. However, how HCV regulates the autophagic pathway remains largely unclear. In this report, we demonstrated that HCV infection could induce the expression of Rubicon and UVRAG, which inhibited and stimulated the maturation of autophagosomes, respectively. The induction of Rubicon by HCV was prompt whereas the induction of UVRAG was delayed, resulting in the accumulation of autophagosomes in the early time points of viral infection. The role of Rubicon in inhibiting the maturation of autophagosomes in HCV-infected cells was confirmed by siRNA knockdown and the over-expression of Rubicon, which enhanced and suppressed the maturation of autophagosomes, respectively. Rubicon played a positive role in HCV replication, as the suppression of its expression reduced HCV replication and its over-expression enhanced HCV replication. In contrast, the over-expression of UVRAG facilitated the maturation of autophagosomes and suppressed HCV replication. The HCV subgenomic RNA replicon, which expressed only the nonstructural proteins, could also induce the expression of Rubicon and the accumulation of autophagosomes. Further analysis indicated that the HCV NS4B protein was sufficient to induce Rubicon and autophagosomes. Our results thus indicated that HCV, by
differentially inducing the expression of Rubicon and UVRAG, temporally regulated the autophagic flux to enhance its replication.

**Evaluation of sequencing of HCV core/E1, NS5A and NS5B as a genotype predictive tool in comparison with commercial assays targeting 5'UTR.**

**BACKGROUND:** Hepatitis C virus (HCV) genotyping is required for tailoring the dose and duration of antiviral therapy, predicting virological response rates, and selecting future treatment options. **OBJECTIVE:** To establish whether baseline genotypes, performed by INNO-LiPA Version 1.0 (v1.0), before 2008, were valid for making treatment decisions now or whether genotypic determination should be repeated. Furthermore, to evaluate concordance between Abbott RealTime genotype II assay (RT) and genotyping by sequencing HCV C/E1, NS5A, NS5B. **STUDY DESIGN:** Genotyping by RT and sequencing was performed on paired historic and current specimens from 50 patients previously baseline genotyped using INNO-LiPA. **RESULTS:** Of 100 samples from 50 patients, ≥2 of HCV genomic target regions yielded a sequence that was suitable for genotyping, with 100% concordance, providing no evidence of recombination events. Genotype and subtype prediction based on RT and sequencing agreed in 62.8% historic and 72.7% current specimens, with a kappa coefficient score of 0.48 and 0.76, respectively. LiPA could not subtype 46% of HCV gt1 infections, and LiPA subgenotype was only in agreement with RT and sequencing in 28.6% cases, where matched baseline and historic specimens were available. Three patients were indeterminate by RT, and five patients with HCV gt1 infections could not be subtyped by RT. However, RT revealed mixed infections in five patients where sequencing detected only single HCV infection at 20% threshold. **CONCLUSION:** Genotyping by sequencing, exhibited excellent concordance, with moderate to good agreement with RT, and could resolve RT indeterminates and subtype HCV-gt1 infections not possible by LiPA.

The hepatitis C virus (HCV) NS3 is a multifunctional protein composed of a protease domain and helicase domain linked by a flexible linker. Protease activity is required to generate viral non-structural (NS) proteins involved in RNA replication. Helicase activity is required for RNA replication and genetic evidence implicates the helicase domain in virus assembly. Binding of protease inhibitors (PIs) to the protease active site blocks NS3-dependent polyprotein processing but might impact other steps of the virus life cycle. Kinetic analyses of antiviral suppression of the cell culture-infectious gt1a strain H77S.3 were performed using assays that measure different readouts of the viral life cycle. In addition to the active site PI telaprevir, we examined an allosteric protease/helicase inhibitor (APHI) that binds a site in the interdomain interface. By measuring nucleotide incorporation into HCV genomes, we found that telaprevir inhibits RNA synthesis as early as 12 hrs, at high but clinically relevant concentrations. Immunoblot analyses showed that NS5B abundance was not reduced until after 12 hrs suggesting that telaprevir exerts a direct effect on RNA synthesis. In contrast, the APHI could partially inhibit RNA synthesis suggesting that the allosteric site is not always available during RNA synthesis. The APHI and active site PI were both able to block virus assembly soon (<12 hrs) after drug treatment.
suggesting that they rapidly engage with and block a pool of NS3 involved in assembly. In conclusion, PIs and APHIs can block NS3 functions in RNA synthesis and virus assembly in addition to inhibiting polyprotein processing. **IMPORTANCE:** The NS3/4A protease of hepatitis C virus (HCV) is an important antiviral target. Currently, three PIs have been approved for therapy of chronic hepatitis C and several others are in development. NS3-dependent cleavage of the HCV polyprotein is required to generate the mature non-structural proteins that form the viral replicase. Inhibition of protease activity can block RNA replication by preventing expression of mature replicase components. Like many viral proteins, NS3 is multifunctional but how PIs affect stages of the HCV life cycle beyond polyprotein processing has not been well studied. Using cell-based assays, we show here that PIs can directly inhibit viral RNA synthesis and also block a late stage in virus assembly/maturation at clinically relevant concentrations.

The ubiquitous ATP-dependent RNA helicase DDX3X is involved in many cellular functions including innate immunity and is a pivotal host factor for hepatitis C virus (HCV) infection. Recently, we showed that DDX3X specifically recognizes HCV 3’ UTR leading to activation of IKK-α and a cascade of lipogenic signaling to facilitate lipid droplet biogenesis and viral assembly. Interaction of DDX3X with HCV core protein seems to be dispensable for its proviral role. In this study, through systematic imaging, biochemical and virologic approaches, we identified a dynamic association between DDX3X and various cellular compartments and viral elements mediating multiple functions of DDX3X in productive HCV infection. Upon HCV infection, HCV 3’ UTR interacts with DDX3X and IKK-α that redistribute to speckle-like cytoplasmic structures shown to be stress granules (SGs). As viral proteins accumulate in infected cells, DDX3X granules together with SG-associated proteins redistribute and co-localize with HCV core protein around lipid droplets (LDs). IKK-α, however, does not relocate to the LD but translocates to the nucleus. In HCV-infected cells, various HCV non-structural proteins also interact or co-localize with DDX3X in close proximity to SGs and LDs, consistent with the tight juxtaposition of the replication complex and the assembly site at the surface of LDs. SiRNA-mediated silencing of DDX3X and multiple SG components markedly inhibits HCV infection. Our data suggest that DDX3X initiates a multifaceted cellular program involving dynamic associations with HCV RNA and proteins, IKK-α, SG and LD surface for its crucial role in HCV life cycle.

**BACKGROUND & AIMS:** Chronic hepatitis C virus infection activates an intrahepatic immune response, leading to increased expression of interferon (IFN)-stimulated genes and activation of natural killer (NK) cells—the most prevalent innate immune cell in the liver. We investigated whether the elimination of HCV with direct-acting antiviral agents normalizes expression of IFN-stimulated genes and NK cell function. **METHODS:** We used multicolor flow cytometry to analyze NK cells from liver and blood of 13 HCV-infected patients who did not respond to treatment with pegylated interferon and ribavirin. Samples were collected before
and during IFN-free treatment with daclatasvir and asunaprevir therapy and compared with those from blood of 13 healthy individuals (controls). Serum levels of CXCL10 and CXCL11 were measured by ELISA. **RESULTS:** Before treatment, all patients had increased levels of CXCL10 or CXCL11 and a different NK cell phenotype from controls, characterized by increased expression of HLA-DR, NKp46, NKG2A, CD85j, pSTAT1, STAT1, and TNF-related apoptosis-inducing ligand (TRAIL). NK cells from patients also had increased degranulation and decreased production of IFNγ and TNFα compared with NK cells from controls. Nine patients had an end-of-treatment response (undetectable virus) and 4 had virologic breakthrough between weeks 4 and 12 of therapy. A rapid decrease in viremia and level of inflammatory cytokines in all patients was associated with decreased activation of intrahepatic NK cells within 24 hours of therapy; it was followed by restoration of a normal NK cell phenotype and function by week 8 in patients with undetectable viremia. This normalized NK cell phenotype was maintained until week 24 (EOT). **CONCLUSIONS:** DAA-mediated clearance of HCV is associated with loss of intrahepatic immune activation by IFNα, indicated by decreased levels of CXCL10 and CXCL11 and normalization of NK cell phenotype and function.


The 63 amino acid polytopic membrane protein, p7, encoded by hepatitis C virus (HCV) is involved in the modulation of electrochemical gradients across membranes within infected cells. Structural information relating to p7 from multiple genotypes has been generated in silico (e.g. genotype (GT) 1a), as well as obtained from experiments in form of monomeric and hexameric structures (GTs 1b and 5a, respectively). However, sequence diversity and structural differences mean that comparison of their channel gating behaviour has not thus far been simulated. Here, a molecular model of the monomeric GT 1a protein is optimized and assembled into a hexameric bundle for comparison with both the 5a hexamer structure and another hexameric bundle generated using the GT 1b monomer structure. All bundles tend to turn into a compact structure during molecular dynamics (MD) simulations (Gromos96 (ffG45a3)) in hydrated lipid bilayers, as well as when simulated at 'low pH', which may trigger channel opening according to some functional studies. Both GT 1a and 1b channel models are gated via movement of the parallel aligned helices, yet the scenario for the GT 5a protein is more complex, with a short N-terminal helix being involved. However, all bundles display pulsatile dynamics identified by monitoring water dynamics within the pore.


**BACKGROUND:** The interaction between hepatitis C virus (HCV) and cellular immune responses during very early infection is critical for disease outcome. To date the impact of antigen-specific cellular immune responses on the evolution of the viral population establishing infection, and potential escape has not been studied. Understanding these early host-virus dynamics is important for the development of a preventative vaccine. **METHODS:** Three subjects followed longitudinally from viremia identified pre-seroconversion until disease outcome were analyzed. The evolution of transmitted/founder (T/F) viruses was undertaken using deep sequencing. CD8+ T cell responses were measured via ELISpot using HLA class I
restricted T/F epitopes. RESULTS: T/F viruses were rapidly extinguished in all subjects associated either with viral clearance (n=1) or replacement with viral variants leading to establishment of chronic infection (n=2). CD8+ T cell responses against 11 T/F epitopes were detectable by 33-44 days post-infection, of which five had not previously been reported. These responses declined rapidly in those who became chronically infected, and were maintained in the subject who cleared infection. Higher magnitude CD8+ T cell responses were associated with rapid development of immune escape variants at a rate up to 0.1 mutations/day.

CONCLUSION: Rapid escape from CD8+ T cell responses has been quantified for the first time in the early phase of primary HCV infection. These rapid escape dynamics were associated with higher magnitude CD8+ T cell responses. These findings raise questions regarding optimal selection of immunogens for HCV vaccine development and suggest detailed analysis of individual epitopes may be required. Importance A major limitation in our detailed understanding of the role of immune response in HCV clearance has been the lack of data on very early primary infection, when the transmitted viral variants successfully establish the acute infection. This study was made possible through the availability of specimens from a unique cohort of asymptomatic primary infection cases, in who the first available viremic sample were collected approximately three weeks post-infection, and at regular intervals thereafter. The study included detailed examination of both the evolution of the viral population and host cellular immune responses against the T/F viruses. The findings here provide the first evidence of host cellular responses targeting T/F variants and imposing a strong selective force towards viral escape. The results of this study provide useful insight on how virus escape the host response, and consequently on future analysis of vaccine-induced immunity.


BACKGROUND: Genome-wide association studies have revealed several single-nucleotide polymorphisms around interleukin 28B (IL28B) that are strongly associated with hepatitis C virus (HCV) clearance. However, their predictive value is not perfect, which suggests that other genetic factors may also be involved in HCV clearance. We previously reported a wide variation in the length of a thymine-adenine (TA) dinucleotide repeat in the promoter region of IL28B and that the transcriptional activity of the promoter increased gradually in a TA repeat length-dependent manner. METHODS: We determined the length of the TA repeats of 1,060 Japanese and 201 African-American samples to investigate the relation to spontaneous HCV clearance.

RESULTS: The distribution of the TA repeats greatly differed between the two ethnicities. The variation ranged from 10 to 18 repeats, and the most frequent allele, 12, accounted for over 80% for Japanese. The African-American data showed a gently sloping distribution, and the allele with six repeats was detected only in the African-American sample. The TA repeats 11 or greater were correlated with spontaneous clearance. Multiple logistic regression analysis extracted the genotype of the TA repeats as an independent factor in both the Japanese [p = 0.0004, odds ratio (OR) = 13.02 95% confidence interval (CI) = 2.59-237.0] and African-American (p = 0.027, OR = 3.70 95% CI = 1.16-11.8) populations. CONCLUSIONS: A long TA repeat in the promoter region of IL28B was associated with spontaneous HCV clearance. Although its efficacy may be limited in Japanese population because of its allele distribution, this novel genetic factor will be useful for predicting HCV clearance especially for the African Americans.
HIV/HCV COINFECTION


BACKGROUND: HIV/hepatitis C virus (HCV) coinfection is associated with reduced bone mineral density (BMD) and increased fracture rates, particularly in women. The structural underpinnings for skeletal fragility in coinfected women have not been characterized. We used tibia peripheral quantitative computed tomography (pQCT) to evaluate skeletal parameters in women, by HIV/HCV status.

METHODS: We conducted a cross-sectional study among 50 HIV/HCV-coinfected, 51 HCV-monoinfected, and 50 HIV-monoinfected women. Tibial volumetric BMD and cortical dimensions were determined by pQCT. Race-specific Z-scores for age were generated using 263 female reference participants without HIV or liver disease.

RESULTS: Coinfected participants had lower mean trabecular volumetric BMD (-0.85), cortical volumetric BMD (-0.67), cortical area (-0.61), and cortical thickness (-0.77) Z-scores than reference participants (all p<0.001). The smaller cortical dimensions were due to greater mean endosteal circumference (+0.67; p<0.001) and comparable periosteal circumference (+0.04; p=0.87) Z-scores. Trabecular volumetric BMD was lower in coinfected than HCV- and HIV-monoinfected participants. HCV-infected women with stage 3-4 liver fibrosis had lower mean trabecular volumetric BMD, cortical thickness, and total hip BMD Z-scores than those with stage 0-2 fibrosis.

CONCLUSIONS: Compared to healthy reference patients, HIV/HCV-coinfected women had decreased tibial trabecular volumetric BMD, diminished cortical dimensions, and significant endocortical bone loss.


Pre-existing low-frequency resistance-associated variants (RAVs) may jeopardize successful sustained virological responses (SVR) to HCV treatment with direct-acting antivirals (DAAs). However, the potential impact of low-frequency (~0.1%) mutations, concatenated mutations (haplotypes), and their association with genotypes (Gts) on the treatment outcome has not yet been elucidated, most probably owing to the difficulty in detecting pre-existing minor haplotypes with sufficient length and accuracy. Herein, we characterize a methodological framework based on Illumina MiSeq next-generation sequencing (NGS) coupled with bioinformatics of quasispecies reconstruction (QSR) to realize highly accurate variant calling and genotype-haplotype detection. The core-to-NS3 protease coding sequences in 10 HCV monoinfected patients, 5 of whom had a history of blood transfusion, and 11 HCV/HIV coinfected patients with hemophilia, were studied. Simulation experiments showed that, for minor variants constituting more than 1%, our framework achieved a positive predictive value (PPV) of 100% and sensitivities of 91.7-100% for genotyping and 80.6% for RAV screening. Genotyping analysis indicated the prevalence of dominant Gt1a infection in coinfected patients (6/11 vs 0/10, p = 0.01). For clinical samples, minor genotype overlapping infection was prevalent in HCV/HIV coinfected hemophiliacs (10/11) and patients who experienced whole-blood transfusion (4/5) but none in patients without exposure to blood (0/5). As for RAV screening, the
Q80K/R and S122K/R variants were particularly prevalent among minor RAVs observed, detected in 12/21 and 6/21 cases, respectively. Q80K was detected only in coinfected patients, whereas Q80R was predominantly detected in monoinfected patients (1/11 vs 7/10, p < 0.01). Multivariate interdependence analysis revealed the previously unrecognized prevalence of Gt1b-Q80K, in HCV/HIV coinfected hemophiliacs [Odds ratio = 13.4 (3.48–51.9), p < 0.01]. Our study revealed the distinct characteristics of viral quasispecies between the subgroups specified above and the feasibility of NGS and QSR-based genetic deconvolution of pre-existing minor Gts, RAVs, and their interrelationships.


**BACKGROUND:** HIV infection leads to lower rates of HCV clearance after acute infection, higher HCV viremia, and accelerated progression of HCV-related fibrosis. The mechanisms underlying this acceleration of HCV progression by HIV are poorly understood, but HIV-induced dysfunction in the anti-HCV humoral immune response may play a role. **METHODS:** To define the effect of HIV coinfection on the anti-HCV antibody response, we measured anti-HCV envelope (E1E2) binding antibody titers, neutralizing antibody (nAb) titers, and neutralizing antibody breadth of serum from HCV-infected subjects isolated longitudinally before and after incident HIV infection. **RESULTS:** A significant reduction in HCV envelope-specific binding antibody and neutralizing antibody titers was detected in subjects with CD4+ T cell counts of <350 cells/mm3 after HIV infection, and subjects with CD4+ T cell counts of <200 cells/mm3 also showed a reduction in nAb breadth. Subjects who maintained ≥350 CD4+ T cells/mm3 displayed little to no decline in antibody levels. **CONCLUSIONS:** Depletion of CD4+ T cells by HIV infection results in a global decline in the anti-HCV envelope antibody response, including binding antibody titers, neutralizing antibody titers, and neutralizing antibody breadth.


**INTRODUCTION:** Single-nucleotide polymorphisms (SNPs) associated with hepatitis C virus (HCV) clearance were identified near the IL28B gene. Coinfection by the human immunodeficiency virus (HIV) influences the course of HCV contributing to liver damage. Nevertheless, little is known about the relationship between these SNPs and HCV/HIV coinfection. Our aim was to estimate the frequencies of the allelic and genotypic variants of the IL28B polymorphisms rs12979860 (C/T) and rs8099917 (T/G) and their possible association with the establishment of HCV infection. **METHODOLOGY:** A total of 199 non-infected controls and 230 patients with chronic hepatitis C, including 53 coinfected with HIV, participated in the study. Genotyping consisted of polymerase chain reaction and subsequent analysis of the restriction patterns resulting from exposure to endonucleases. **RESULTS:** Among the controls with established results, 47.4% (90/190) exhibited the rs12979860 CC genotype, 43.7 CT, and 8.9% TT, whereas 29.1% (66/227), 51.5%, and 19.4% of the patients exhibited the CC, CT, and TT genotypes, respectively. With respect to rs8099917, 66.8% (133/199) of the controls exhibited the TT genotype, 31.2% TG, and 2.0% GG, whereas 56.1% (129/230), 40.9%, and 3.0% of the patients exhibited the TT, TG, and GG genotypes,
respectively. **CONCLUSION:** The frequencies of the rs12979860 C allele and CC genotype and of the rs8099917 T allele and TT genotype were significantly higher among controls compared with patients, thus confirming the suggested protective effect against HCV infection. No significant difference was observed in the genotype and allelic distributions between the mono- and coinfected patients.


**OBJECTIVES:** We have analyzed the parameters (bacterial translocation, immune activation and regulation, presence of HCV coinfecion) which could be implicated in an inappropriate immune response from individuals with chronic HIV infection. The influence of them on the evolution of CD4+ T cell count has been investigated. **PATIENTS AND METHODS:** Seventy HIV-infected patients [monoinfected by HIV (n = 20), HCV-coinfected (with (n = 25) and without (n = 25) liver cirrhosis)] and 25 healthy controls were included. Median duration of HIV infection was 20 years. HIV- and HCV-related parameters, as well as markers relative to bacterial translocation, monocyte and lymphocyte activation and regulation were considered as independent variables. Dependent variables were the increase of CD4+ T cell count during the follow-up (12 months). **RESULTS:** Increased values of bacterial translocation, measured by lipopolysaccharide-binding protein, monocyte and lymphocyte activation markers and T regulatory lymphocytes were detected in HIV-monoinfected and HIV/HCV coinfected patients. Serum sCD14 and IL-6 were increased in HIV/HCV-coinfected patients with liver cirrhosis in comparison with those with chronic hepatitis or HIV-monoinfected individuals. Time with undetectable HIV load was not related with these parameters. The presence of cirrhosis was negatively associated with a CD4+ T cell count increase. **CONCLUSION:** In patients with a chronic HIV infection, a persistent increase of lipopolysaccharide-binding protein and monocyte and lymphocyte modifications are present. HCV-related cirrhosis is associated with more elevated serum concentrations of monocyte-derived markers. Cirrhosis influences the continued immune reconstitution of these patients.

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**COMPLEMENTARY AND ALTERNATIVE MEDICINE**


A thorough phytochemical study of Stereocaulon evolutum was conducted, for the isolation of structurally related atranorin derivatives. Indeed, pilot experiments suggested that atranorin (1), the main metabolite of this lichen, would interfere with the lifecycle of hepatitis C virus (HCV). Eight compounds, including one reported for the first time (2), were isolated and characterized. Two analogs (5, 6) were also synthesized, to enlarge the panel of atranorin-related structures. Most of these compounds were active against HCV, with a half-maximal inhibitory concentration of about 10 to 70 µM, with depsides more potent than monoaromatic phenols. The most effective inhibitors (1, 5 and 6) were then added at different steps of the HCV lifecycle. Interestingly, atranorin (1), bearing an aldehyde function at C-3, inhibited only viral entry, whereas the synthetic compounds 5 and 6, bearing a hydroxymethyl and a methyl function, respectively, at C-3 interfered with viral replication.

**BACKGROUND:** Zinc deficiency has been observed in cirrhosis, but management guidelines do not address screening for zinc deficiency. We aim to determine the prevalence of zinc deficiency in different stages of cirrhosis and to correlate zinc levels with complications of cirrhosis and clinical outcomes. Patients who had a diagnosis of cirrhosis and had serum zinc levels drawn from 2007 to 2011 were identified. Demographics, laboratory data, presence of ascites, encephalopathy, and infection were obtained; Child-Pugh and MELD scores were calculated. Stata software was used for data analysis. A total of 163 patients were included in the study. **RESULTS:** The median serum zinc level was 0.47 mcg/ml (IQR 0.37-0.63); 83% of patients were zinc deficient. Zinc deficiency was more prevalent in patients with Child-Pugh score B or C, and with MELD scores ≥15. Zinc levels were lower in alcoholic, hepatitis C, and cholestatic diseases than in other etiologies of liver disease. Zinc levels correlated with INR (r = -0.56, p < 0.001), bilirubin (r = -0.51, p < 0.001), and albumin (r = 0.68, p < 0.001), and were lower in patients with ascites (0.40 vs. 0.57 mcg/ml, p < 0.001), encephalopathy (0.40 vs. 0.53 mcg/ml, p < 0.001), diuretic use (0.45 vs. 0.535 mcg/ml, p = 0.005), and infection (0.32 vs. 0.51 mcg/ml, p < 0.001). Ascites (p = 0.044) and infection (p = 0.009) were independently associated with zinc levels. Zinc-deficient patients had lower transplant-free survival rates than non-deficient patients. **CONCLUSION:** Zinc deficiency is highly prevalent in cirrhotic patients with Child-Pugh score B or C, and with MELD score ≥15. Zinc deficiency also correlates with disease severity, infection, and a worse transplant-free survival. Screening for zinc deficiency should be considered in this subset of patients.


Sofosbuvir (SOVALDI®), a potent, once-daily, orally administered nucleotide analog prodrug inhibitor of the hepatitis C virus (HCV) NS5B polymerase is approved in the USA, EU, Canada, and other regions for the treatment of HCV infection as a component of an antiviral treatment regimen. Sofosbuvir undergoes intracellular activation to form GS-461203 (active triphosphate, not detected in plasma), and ultimately the inactive, renally eliminated metabolite GS-331007. GS-331007 was identified as the primary analyte of interest for clinical pharmacology studies as it accounted for >90% of systemic drug-related material exposure, and provided comparable exposure-response relationships for viral kinetics as observed for sofosbuvir. GS-331007 and sofosbuvir exhibit linear pharmacokinetics with minimal accumulation upon multiple dosing. Compared to healthy subjects, HCV-infected patients had modestly lower (39%) GS-331007 area under the plasma concentration-time curve (AUC) and higher sofosbuvir AUC (60%). Sofosbuvir can be administered without dose modification in HCV-infected patients with any degree of hepatic impairment or mild to moderate renal impairment. Sofosbuvir has a low propensity for clinically significant drug interactions with common concomitant medications used by HCV-infected patients. Clinically significant alterations in GS-331007 or sofosbuvir exposures are limited to potent inducers of intestinal P-glycoprotein that may lower exposure. In HCV-infected patients, demographic variables do not significantly influence GS-331007 and
sofosbuvir exposures and no consistent exposure-response relationships were observed for efficacy or safety. This review focuses on the clinical pharmacokinetics, pharmacodynamics, and pharmacokinetic-pharmacodynamic relationships of sofosbuvir, and summarizes a number of drug interaction studies with important concomitant medications commonly used by HCV-infected patients.


**OBJECTIVES:** We investigated whether eventual causes of death among a cohort of inmates imprisoned in the southeastern United States differed from those in previous prisoner studies. 

**METHODS:** We matched 23,510 prisoners in Georgia, a state with historically low levels of heroin consumption but moderate amounts of injection drug use, who were incarcerated on June 30, 1991, to death registries through 2010. Main exposure was 4-year time intervals over 2 decades of observation; main outcome was mortality from liver disease, HIV, and overdose. 

**RESULTS:** Although the HIV-related mortality rate exceeded that from liver-related conditions before 2003, liver disease subsequently surpassed HIV as a cause of death. Among 3,863 deaths, 22 (0.6%) occurred within 2 weeks after release from prison. Of these, only 2 were caused by accidental poisoning (likely drug overdose). Cardiovascular disease and cancer were the most frequent causes of death in this aging cohort. 

**CONCLUSIONS:** Our study design deemphasized immediate deaths but highlighted long-term sequelae of exposure to viral hepatitis and alcohol. Treating hepatitis C and implementing interventions to manage alcohol use disorders may improve survival among prisoners in the Southeast.


**BACKGROUND:** African Americans are disproportionately affected by hepatitis C (HCV) and are less likely to undergo HCV treatment. Underserved populations are especially at risk for experiencing health disparity. Aim. To identify reasons for HCV non-treatment among underserved African Americans in a large safety net system. 

**MATERIAL AND METHODS:** Medical records of HCV-infected African Americans evaluated at San Francisco General Hospital liver specialty clinic from 2006-2011 who did not receive HCV treatment were reviewed. Treatment eligibility and reasons for non-treatment were assessed. Factors associated with treatment ineligibility were assessed using logistic regression modeling. 

**RESULTS:** Among 118 patients, 42% were treatment ineligible, 18% treatment eligible, and 40% were undergoing work-up to determine eligibility. Reasons for treatment ineligibility were medical (54%), non-medical (14%), psychiatric (4%), or combined (28%). When controlling for age and sex, active/recent substance abuse (OR 6.65, p = 0.001) and having two or more medical comorbidities (OR 3.39, p = 0.005) predicted treatment ineligibility. Excluding those ineligible for treatment, 72% of all other patients were lost to follow-up; they were older (55 vs. 48 years, p = 0.01) and more likely to be undergoing work up to determine treatment eligibility (86 vs. 21%, p < 0.0001) than those not lost to follow-up. 

**CONCLUSIONS:** Medical comorbidities and substance abuse predicted HCV treatment ineligibility in underserved African Americans. Importantly, the majority of those undergoing work-up to determine HCV treatment eligibility...
were lost to follow-up. While newer anti-HCV agents may increase treatment eligibility, culturally appropriate interventions to increase compliance with evaluation and care remain critical to HCV management in underserved African Americans.


Persons who inject drugs (PWID) are at high risk for infection with and poor outcomes from HIV and hepatitis C virus (HCV). Well-established interventions for HIV/HCV prevention among PWID include syringe access, opioid agonist maintenance treatment, and supervised injection facilities, yet these interventions remain unavailable or inadequately resourced in much of the world. We review recent literature on biomedical and behavioral interventions to reduce the burden of HIV/HCV among PWID, with an emphasis on randomized controlled trials and quasi-experimental studies. Since 2013, there have been significant advancements in utilizing antiviral therapy and behavioral interventions for prevention among PWID, including approaches that address the unique needs of couples and sex workers. In addition, there have been significant developments in pharmacotherapies for substance use and the implementation of naloxone for opioid overdose prevention. Notwithstanding multiple ongoing structural challenges in delivering HIV/HCV prevention interventions to PWID, these emerging and rigorously evaluated interventions expand possibilities for prevention among PWID.


**OBJECTIVE:** To describe chronic hepatitis C virus (HCV) infection, including its epidemiology and pathophysiology; review current treatment options for HCV infection; recognize investigational agents being studied as part of interferon-free therapy; and summarize clinical trials for the new agents. **DATA SOURCES:** PubMed for 2004 through August 2014 using search terms hepatitis C, American Association for the Study of Liver Diseases, sofosbuvir, simeprevir, and as needed specific names of other agents in development during this time; news articles and news releases about company actions with regard to clinical trials and filings for marketing approval in the United States. **STUDY SELECTION:** At the discretion of the author based on clinical relevance of study and relevance to national guidelines for HCV therapy. **RESULTS:** HCV infection is an important medical and public health problem in the United States and worldwide that can cause cirrhosis, hepatocellular carcinoma, and liver failure. The advent of newly developed targeted therapies is changing the treatment paradigm for this disease. Although traditional therapy with pegylated interferon and ribavirin remain therapeutic options, direct-acting agents such as sofosbuvir (Sovaldi-Gilead) and simeprevir (Olysio-Janssen) are producing faster, earlier, and improved treatment response with fewer adverse effects. The combination of anti-HCV agents and the duration of treatment are based on genotype, patient treatment status, and patient risk factors. The dramatic and sustained clearance of the virus with these drugs makes sustained virologic response a reality for patients who are unable to tolerate pegylated interferon. The downside is their high cost, which may make them economically unsustainable. However, for patients infected with HCV, the potential for a cure and improved quality of life may now be a reality. **CONCLUSION:** HCV, a well-known blood-borne disease associated with significant morbidity and mortality worldwide, can be effectively
and safely treated with new anti-HCV agents such as SOF. While these new medications are in their early days of real-world practice, they offer hope that cure is truly possible.


Hepatitis C treatment is rapidly evolving with significant improvements in patient outcomes. With an estimated prevalence of over 3 million persons living with chronic hepatitis C in the United States, it is anticipated that there will be an increase in the number of persons seeking care and treatment for chronic hepatitis C infection. Current systems of care may be overburdened with people seeking care for chronic hepatitis C virus (HCV). Interprofessional models of care have been shown to be feasible and effective in treating different populations affected by chronic HCV. Use of interprofessional teams, integrated models of care, and greater use of nonphysician providers offer a potential solution for expanding capacity to comprehensive HCV treatment and care in the United States.


OBJECTIVE: Depressive symptoms have been frequently observed in association with immune activation. We prospectively evaluate depressive symptoms and risk factors for major depression in patients with hepatitis C virus treated with antiviral combined therapy. METHODS: Fifty patients were assessed during 1 year; the structured diagnostic interview - Mini International Neuropsychiatric Interview - was used to screen psychiatric disorders at the baseline and during the 4th and 12th week of antiviral therapy. STATISTICAL ANALYSIS: generalized estimating equations and pairwise comparisons with Bonferroni adjustment. RESULTS: In our sample the prevalence of the Genotype 1 was 42%, and the pegylated interferon alpha plus ribavirin was the most prevalent treatment used for hepatitis C (86%). We found increased risk of depression in the 4th week (34%) but not in the 12th week (24%) compared with baseline values (20%) (P=0.040). In addition, we found differences between depression prevalence and hepatitis C genotypes, with higher odds in the 4th week compared to the baseline and 12th week [OR: 2.1(1.15-2.9); P=0.040]. Patients with the Genotype 2/3 had significantly lower odds of presenting depression compared to the Genotype 1 [OR: 0.3 (0.1-0.9); P=0.030]. CONCLUSION: This study provides evidence for an association between hepatitis C genotype and major depression, showing that besides immune activation, the Genotype 1 is associated with increased risk for psychiatric symptoms during the follow-up.

LIVER CANCER


PURPOSE: The incidence of hepatocellular carcinoma (HCC) in patients with nonalcoholic fatty liver disease (NAFLD) is increasing. However, the clinicopathological features of HCC in these patients are little known. Thus, we investigated the differences in the clinical and
pathological characteristics of HCC between NAFLD patients and hepatitis-C virus (HCV) patients. METHODS: Data from 21 HCC patients with NAFLD and 645 HCC patients with HCV who underwent curative hepatectomy were collected and analyzed. To overcome bias due to differences in the distribution of covariates between the two groups, propensity score matching was performed, and clinicopathological features and outcomes were compared. RESULTS: In propensity score analysis, the rate of microscopic vascular invasion was significantly higher in the NAFLD group than in the HCV group (65 vs. 30 %; P = 0.027). However, overall survival and disease-free survival did not differ between the two matched groups. CONCLUSIONS: NAFLD may have permissive microenvironment for HCC progression.

A comparison of the surgical outcomes among patients with HBV-positive, HCV-positive, and non-B non-C hepatocellular carcinoma: a nationwide study of 11,950 patients. Utsunomiya T1, Shimada M, Kudo M, et al. Ann Surg. 2015 Mar;261(3):513-20. doi: 10.1097/SLA.0000000000000821. OBJECTIVE: To compare the prognostic factors and outcomes after hepatic resection among patients with hepatitis B virus (HBV)-positive, hepatitis C virus (HCV)-positive, and negative for hepatitis B surface antigen and hepatitis C antibody, so-called "NBNC"-hepatocellular carcinoma (HCC) using the data from a nationwide survey. BACKGROUND: The incidence of NBNC-HCC is rapidly increasing in Japan. METHODS: A total of 11,950 patients with HBV-HCC (n = 2194), HCV-HCC (n = 7018), or NBNC-HCC (n = 2738) who underwent a curative hepatic resection were enrolled in this study. The clinicopathological features were compared among the groups. The significant prognostic variables determined by univariate analysis were subjected to a multivariate analysis using a Cox proportional hazard regression model. RESULTS: Liver function in the HCV-HCC group was significantly worse than that in the HBV-HCC and NBNC-HCC groups. The NBNC-HCC group had significantly more advanced HCC than the HCV-HCC group. The 5-year overall survival rates after hepatectomy in the HBV-HCC, HCV-HCC, and NBNC-HCC groups were 65%, 59%, and 68%, respectively. The 5-year recurrence-free survival (RFS) rates in these 3 groups were 41%, 31%, and 47%, respectively. Stratifying the RFS rates according to the TNM stage showed that the NBNC-HCC group had a significantly better prognosis than the HBV-HCC group in stages II, III, and IVA, and a significantly better prognosis than the HCV-HCC group in stages I and II. Multivariate analysis revealed a significantly better RFS rate in the NBNC-HCC group. CONCLUSIONS: The findings of this nationwide survey indicated that patients with NBNC-HCC had a significantly lower risk of HCC recurrence than those with HBV-HCC and HCV-HCC.

The "Macro" World of microRNAs in Hepatocellular Carcinoma. Sidhu K1, Kapoor NR1, Pandey V1, Kumar V1. Front Oncol. 2015 Mar 25;5:68. doi: 10.3389/fonc.2015.00068. eCollection 2015. Hepatotropic viruses such as hepatitis B virus (HBV) and hepatitis C virus (HCV) are the major etiological agents associated with development of hepatocellular carcinoma (HCC). Progression of HCC is a multistep process that requires sequential or parallel deregulation of oncogenic and tumor suppressive pathways leading to chromosomal instability and neoplastic phenotype. In the recent years, microRNAs (miRNAs) have carved their own niche alongside oncogenes and tumor suppressors, owing to their innate ability to receive and relay multiple signals. Not surprisingly, miRNAs are fast emerging as central player in myriads of malignancies including
miRNAs are reported to participate in initiation and progression of HCC, and have also been clinically correlated with risk assessment, disease grade, aggressiveness, and prognosis. Despite extensive data available on the role of miRNAs in HCC, there is a pressing need to integrate and evaluate these datasets to find its correlation, if any, with causal agents in order to devise novel interventional modalities. Through this review, we attempt to bridge the gap by consolidating the current knowledge and concepts in the field of HCC-related miRNAs with special emphasis on HBV and HCV. Further, we assess the potential of common as well as unique signatures that may be useful in developing novel biomarkers and therapeutics.


The purpose of this study was to evaluate the diagnostic efficiency for hepatocellular carcinoma (HCC) with the combined analysis of alpha-L-fucosidase (AFU), alpha-fetoprotein (AFP) and thymidine kinase 1 (TK1). Serum levels of AFU, AFP and TK1 were measured in: 116 patients with HCC, 109 patients with benign hepatic diseases, and 104 normal subjects. The diagnostic value was analyzed using the logistic regression equation and receiver operating characteristic curves (ROC). Statistical distribution of the three tested tumor markers in every group was non-normally distributed (Kolmogorov-Smirnov test, Z = 0.156-0.517, P < 0.001). The serum levels of AFP and TK1 in patients with HCC were significantly higher than those in patients with benign hepatic diseases (Mann-Whitney U test, Z = -8.570 to -5.943, all P < 0.001). However, there was no statistically significant difference of AFU between these two groups (Mann-Whitney U test, Z = -1.820, P = 0.069). The levels of AFU were significantly higher in patients with benign hepatic diseases than in normal subjects (Mann-Whitney U test, Z = -7.984, P < 0.001). Receiver operating characteristic curves (ROC) in patients with HCC versus those without HCC indicated the optimal cut-off value was 40.80 U/L for AFU, 10.86 μg/L for AFP and 1.92 pmol/L for TK1, respectively. The area under ROC curve (AUC) was 0.718 for AFU, 0.832 for AFP, 0.773 for TK1 and 0.900 for the combination of the three tumor markers. The combination resulted in a higher Youden index and a sensitivity of 85.3%. The combined detection of serum AFU, AFP and TK1 could play a complementary role in the diagnosis of HCC, and could significantly improve the sensitivity for the diagnosis of HCC.


Hepatocellular carcinoma (HCC) is one of the most common and lethal cancers in the world, with limited options for treatment unless timely diagnosed. Chronic hepatitis C virus (HCV) infection and persistent heavy alcohol consumption are independent risk factors for HCC development, which may induce a specific protein expression pattern different from those caused separately. The aim of the study was to identify protein biomarkers for the detection of HCC in HCV-infected alcoholic patients with cirrhosis in order to improve survival. We compared protein expression profiles of plasma samples from 52 HCV-infected alcoholic patients with and without HCC, using 2-D DIGE coupled with MALDI-TOF/TOF mass spectrometry. The 2-D DIGE results were analyzed statistically using Decyder software, and verified by western-blot and ELISA. In plasma samples from HCV-infected alcoholic patients, we found significantly
differential expression profiles of carboxypeptidase-N, ceruloplasmin (CP), complement component 4a (C4a), fibrinogen-alpha (FGA), immunoglobulin mu chain C region, serum albumin, and serum paraoxonase/arylesterase 1 (PON1). Deregulation of plasma/serum levels of the identified proteins was associated to HCV, ethanol consumption, and/or HCC progression. In the validation through ELISA, C4a serum concentration was increased in HCC patients (2.4±1 ng/mg vs 1.8±0.6 ng/mg; p = 0.029), being the only independent predictor of HCC in the multivariate analysis (OR = 2.15; p = 0.015), with an AUROC = 0.70. The combination of C4a, FGA, CP and PON1 improved slightly the predictive ability of C4a alone (AUROC 0.81). In conclusion, we identified proteins related to acute-phase response, oxidative stress, or immune response, whose differential expression in plasma may be attributed to the presence of HCC. Among them, C4a, and its combination with CP, FGA and PON1, could be considered as potentially reliable biomarkers for the detection of HCC in HCV-infected alcoholic patients.


BACKGROUND & AIMS: Hepatocellular carcinoma (HCC) is the second most common cause of cancer deaths worldwide. The global HCC BRIDGE study was a multiregional, large-scale, longitudinal cohort study undertaken to improve understanding of real-life management of patients with HCC, from diagnosis to death. METHODS: Data were collected retrospectively from January 2005 to September 2012 by chart reviews of eligible patients newly diagnosed with HCC at participating institutions. RESULTS: Forty-two sites in 14 countries contributed final data for 18,031 patients. Asia accounted for 67% of patients, Europe for 20% and North America for 13%. As expected, the most common risk factor was hepatitis C virus in North America, Europe and Japan, and hepatitis B virus in China, South Korea and Taiwan. The most common Barcelona Clinic Liver Cancer stage at diagnosis was C in North America, Europe, China and South Korea, and A in Taiwan and Japan. Across all stages, first HCC treatment was most frequently transarterial chemoembolization in North America, Europe, China and South Korea, percutaneous ethanol injection or radiofrequency ablation in Japan and resection in Taiwan. Survival from first HCC treatment varied significantly by region, with median overall survival not reached for Taiwan and 60, 33, 31, 24 and 23 months for Japan, North America, South Korea, Europe and China respectively (P < 0.0001). CONCLUSIONS: Initial results from the BRIDGE study confirm previously reported regional trends in patient demographic characteristics and HCC risk factors, document the heterogeneity of treatment approaches across regions/countries and underscore the need for earlier HCC diagnosis worldwide.