
PURPOSE: To investigate the status of the blood-aqueous barrier and to evaluate the subfoveal choroidal thickness (SCT) in patients with asymptomatic untreated chronic hepatitis C virus (HCV) infection without any anterior or posterior ocular involvement and to search for possible correlations. DESIGN: Observational case-control study. PARTICIPANTS AND CONTROLS: A total of 80 eyes of 20 HCV-positive patients (male-to-female ratio, 12:8; mean age, 46.9±7.23 years) and 20 healthy controls (male-to-female ratio, 10:10; mean age, 48.2±8.71 years) were examined. METHODS: Participants underwent a complete ophthalmologic examination. Aqueous flare was quantified objectively by using the noninvasive laser flare cell meter FC-500 (Kowa Company Ltd, Tokyo, Japan), whereas SCT was evaluated by using enhanced depth imaging optical coherence tomography (Spectralis OCT; Heidelberg Engineering GmbH, Heidelberg, Germany). A Wilcoxon rank-sum test was performed to compare ocular findings between HCV patients and controls, and correlations were assessed by using the Spearman rank test. MAIN OUTCOME MEASURES: Retinal and choroidal thickness and anterior chamber inflammation of HCV patients and healthy controls. RESULTS: Patients with HCV showed significantly higher aqueous flare values (8.37±2.25 photon counts/ms vs. 4.56±1.45 photon counts/ms; P<0.0001) and a significantly increased SCT (362.7±46.5 μm vs. 320.25±32.82 μm; P<0.0001) than healthy controls. Moreover, subjects with liver fibrosis had higher flare values than those with no significant hepatic fibrosis (9.62±1.99 photon counts/ms vs. 6.97±2.19 photon counts/ms; P = 0.0003) and thicker choroids (379.15±44.75 μm vs. 346.3±43.27 μm; P = 0.024). Statistical analysis revealed that there was a positive correlation between aqueous flare values and SCT in HCV patients (r = 0.69; P<0.0001) and between flare and the degree of liver fibrosis (r = 0.67; P = 0.0001). CONCLUSIONS: This study showed that impairment of the blood-aqueous barrier and thickened choroids are features of asymptomatic HCV patients, and that choroidal thickness increases as the degree of subclinical inflammation of the anterior chamber increases. Patients with significant liver fibrosis have the highest flare values and the thickest choroids.
This study aimed to determine the most suitable duration of pegylated-interferon (Peg-IFN)-plus-ribavirin combination therapy in patients infected with hepatitis C virus (HCV) genotype 2 who had not achieved rapid virological response (serum HCV RNA disappearance after 4 weeks of therapy). HCV genotype 2 patients (n = 182) with a high viral load received >80% of the standard Peg-IFN-plus-ribavirin dose for at least 24 weeks, and their final virological responses were studied. Patients were classified into "rapid virological response" and "non-rapid virological response" groups. The non-rapid virological response group was further divided into a "virological response at 8 weeks" (serum HCV RNA disappearance after 8 weeks of therapy) and a "non-virological response at 8 weeks" group. Factors related to rapid virological response and optimal therapy duration in the non-rapid virological response group were evaluated. Multivariate logistic regression analysis showed that subtype HCV genotype 2a (P = 0.0015) and low concentration of pretreatment serum HCV RNA (P = 0.0058) were independent factors in a rapid virological response. In the virological response at 8 weeks group, the sustained virological response rate after 24 weeks of therapy was significantly lower than after 36 weeks (P = 0.044) or after 48 weeks (P = 0.006), and was similar for 36- and 48-weeks. The cost for achieving (CAS) one sustained virological response was lowest with 36-week therapy. Prolongation of Peg-IFN-plus-ribavirin combination therapy to 36 weeks is suitable for achieving virological response at 8 weeks, given the high, sustained virological response rate and cost benefit.

BACKGROUND: The partially-blinded, randomized, phase IIa C210 study evaluated the antiviral activity of telaprevir-based regimens in treatment-naive, genotype 4 chronic hepatitis C virus (HCV)-infected patients. METHODS: Patients (n=24) received 15 days of telaprevir 750 mg every 8 hours (T; n=8), telaprevir in combination with peginterferon alfa-2a and ribavirin (Peg-IFN/RBV; TPR; n=8), or Peg-IFN/RBV plus placebo (PR; n = 8), followed by Peg-IFN/RBV for 46 or 48 weeks. The primary objective was to assess the effect of telaprevir on HCV RNA levels. RESULTS: HCV RNA levels decreased slightly with T and PR; TPR produced substantial, rapid declines. At Day 15, median HCV RNA reductions from baseline were -0.77, -4.32, and -1.58 log10 IU/mL for T, TPR and PR, respectively, and 0 (T), 1 (TPR), and 0 (PR) patients had undetectable HCV RNA. Five/eight patients who received telaprevir monotherapy had viral breakthrough within 15 days of treatment. Adverse event incidence was similar across treatments and comparable with previous clinical trials. One patient (T group) had a serious adverse event (considered unrelated to telaprevir) that led to treatment discontinuation. CONCLUSIONS: Telaprevir with Peg-IFN/RBV had greater activity against HCV genotype 4 than Peg-IFN/RBV or telaprevir monotherapy. Telaprevir was generally safe and well tolerated. Further investigation of telaprevir combination therapy in genotype 4 patients is warranted.

**BACKGROUND:** Chronic Hepatitis C virus (HCV) infection has been suggested to be associated with non insulin dependent diabetes mellitus (NIDDM) and lipid profiles. This study aimed to investigate the possible relationships of insulin resistance (IR) and lipid profiles with chronic hepatitis C (CHC) patients in Taiwan. **METHODS:** We enrolled 160 hospital-based CHC patients with liver biopsy and the 480 controlled individuals without CHC and chronic hepatitis B from communities without known history of NIDDM. Fasting plasma glucose (FPG), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), alanine aminotransferase (ALT) and serum insulin levels and homeostasis model assessment (HOMA-IR) were tested. **RESULTS:** When comparing factors between CHC patients and sex- and age-matched controls who had no HCV infection, patients with HCV infection had a significantly higher ALT level, FPG level, insulin level, and HOMA-IR (P<0.001, P=0.023, P=0.017 and P= 0.011, respectively) and significantly lower triglycerides level (P=0.023), total cholesterol, HDL-C and LDL-C levels (all Ps<0.001) than 480 controls. In multivariate logistic regression analyses, a low total cholesterol, a low triglycerides and a high HOMA-IR are independent factors significantly associated with chronic HCV Infection. In the 160 CHC patients [41 patients with high HOMA-IR (>2.5)], a high BMI, triglycerides and HCV RNA level are independent factors significantly associated with high HOMA-IR in multivariate logistic analyses. **CONCLUSIONS:** Chronic HCV infection was associated with metabolic characteristics including IR and lipid profile. IR was also associated with virological characteristics.


**Background:** T-cell responses have been described in seronegative patients who test negative for hepatitis C virus (HCV) RNA despite frequent HCV exposure. However, the cross-sectional design of those studies did not clarify whether T cells were indeed induced by low-level HCV exposure without seroconversion or whether they resulted from regular acute infection with subsequent antibody loss. **METHODS:** Over a 10-year period, our longitudinal study recruited 72 healthcare workers with documented HCV exposure. We studied viremia and antibody and T-cell responses longitudinally for 6 months. **RESULTS:** All healthcare workers remained negative for HCV RNA and antibodies. However, 48% developed proliferative T-cell response and 42% developed responses in interferon-gamma enzyme-linked immunosorbent spot assays, with 29 healthy HCV-unexposed controls used to define assay cutoffs. The response prevalence was associated with the transmission risk score. T-cell responses peaked at week 4 and returned to baseline by week 12 after exposure. They predominantly targeted nonstructural HCV proteins, which are not part of the HCV particle and thus must have been synthesized in infected cells. **CONCLUSIONS:** Subclinical transmission of HCV occurs frequently, resulting in infection and synthesis of nonstructural proteins despite undetectable systemic viremia. T-cell responses are more sensitive indicators of this low-level HCV exposure than antibodies.

Faldaprevir (BI 201335) is a potent, hepatitis C virus (HCV) NS3/4A protease inhibitor. In all, 290 noncirrhotic HCV genotype (GT)-1 patients with prior null (<1 log10 viral load [VL] drop at any time on treatment) or partial response (≥1 log10 VL drop but never undetectable on treatment) were randomized 2:1:1 to receive 48 weeks of peginterferon alfa-2a and ribavirin (PegIFN/RBV) in combination with faldaprevir 240 mg once daily (QD) with 3 days PegIFN/RBV lead-in (LI), 240 mg QD without LI, or 240 mg twice daily (BID) with LI. Patients in the 240 mg QD/LI group achieving maintained rapid virologic response (mRVR; VL <25 IU/mL [Roche TaqMan] at week 4 and undetectable at weeks 8 to 20) were rerandomized to cease all treatment at week 24 or continue PegIFN/RBV up to week 48. Sustained virologic response (SVR) rates were 32%, 50%, and 42% in prior partial responders, and 21%, 35%, and 29% in prior null responders in the faldaprevir 240 mg QD/LI, 240 mg QD, and 240 mg BID/LI groups, respectively. In the 240 mg QD/LI group, a significantly higher proportion of mRVR patients rerandomized to 48 weeks’ treatment achieved SVR compared with those assigned to 24 weeks treatment (72% versus 43%; P = 0.035). Rates of gastrointestinal disorders, jaundice, dry skin, and photosensitivity were increased at 240 mg BID compared with the 240 mg QD dose. Faldaprevir discontinuations owing to adverse events occurred in 6%, 4%, and 23% of patients in the 240 mg QD/LI, 240 mg QD, and 240 mg BID/LI groups, respectively. CONCLUSION: Faldaprevir 240 mg QD with PegIFN/RBV was safe and tolerable and produced substantial SVR rates in prior null and partial responders. The 240 mg QD dose is currently undergoing phase 3 evaluation.


Faldaprevir (BI 201335) is a potent, hepatitis C virus (HCV) NS3/4A protease inhibitor with pharmacokinetic properties supportive of once-daily (QD) dosing. Four hundred and twenty-nine HCV genotype (GT)-1 treatment-naïve patients without cirrhosis were randomized 1:1:2:2 to receive 24 weeks of pegylated interferon alfa-2a and ribavirin (PegIFN/RBV) in combination with placebo, faldaprevir 120 mg QD with 3 days of PegIFN/RBV lead-in (LI), 240 mg QD with LI, or 240 mg QD without LI, followed by an additional 24 weeks of PegIFN/RBV. Patients in the 240 mg QD groups achieving maintained rapid virologic response (mRVR; viral load [VL] <25 IU/mL at week 4 and undetectable at weeks 8-20) were rerandomized to cease all treatment at week 24 or continue receiving PegIFN/RBV up to week 48. VL was measured by Roche TaqMan. Sustained virologic response (SVR) rates were 56%, 72%, 72%, and 84% in the placebo, faldaprevir 120 mg QD/LI, 240 mg QD/LI, and 240 mg QD groups. Ninety-two percent of mRVR patients treated with faldaprevir 240 mg QD achieved SVR, irrespective of PegIFN/RBV treatment duration. Eighty-two percent of GT-1a patients who received faldaprevir 240 mg QD achieved SVR versus 47% with placebo. Mild gastrointestinal disorders, jaundice resulting from isolated unconjugated hyperbilirubinemia, and rash or photosensitivity were more common in the active groups than with placebo. Discontinuations resulting from adverse events occurred in 4%, 11%, and 5% of patients treated with 120 mg QD/LI, 240 mg QD/LI, and 240 mg QD of faldaprevir versus 1% with placebo. CONCLUSION: Faldaprevir QD with...
PegIFN/RBV achieved consistently high SVR rates with acceptable tolerability and safety at all dose levels. The 120 and 240 mg QD doses are currently undergoing phase 3 evaluation.


**BACKGROUND:** Chronic hepatitis C virus (HCV) infection and its treatment impact patients' health-related quality of life (HRQL). **AIM:** To report on treatment impact and predictors of HRQL among treatment-naïve patients with genotype 1 chronic HCV infection who received 12-week telaprevir (T) with 24 (T12PR24) or 48 weeks (T12PR48) peginterferon alpha-2a/ribavirin (PR), or 48 weeks of PR in the ADVANCE study. **METHODS:** The EQ-5D-3L (EQ-5D) questionnaire (index range: 0-1) was completed at baseline and weeks 4, 12, 24, 36, 48 and 72. Patients indicated their health state on five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Descriptive statistics for the EQ-5D index and descriptive system and area under the curve from baseline to week 12 were calculated. Predictors of EQ-5D index were identified using multivariate analyses. **RESULTS:** Data from 722 patients were included. The mean EQ-5D index decreased during the first 12 weeks and returned to baseline by week 72 (T12PR24 by week 36) across treatments. In multivariate analysis, sustained virological response (SVR) at week 72 was associated (P < 0.0001) with improved EQ-5D index [mean; SVR+ (0.90), SVR- (0.86)], a 4% difference, within the published range of minimal clinically important difference. **CONCLUSIONS:** Post hoc analyses of data from ADVANCE suggested that HRQL worsened during the first 12 weeks of therapy and returned to baseline by week 72 across treatments. Improvements were observed early following completion of a 24-week treatment (T12PR24). Telaprevir combination therapy was associated with slightly higher reductions in HRQL during the first 12 weeks (vs. PR). SVR was a statistically significant and meaningful predictor of HRQL at week 72.


In clinical trials with telaprevir (TLV) and boceprevir (BOC) renal impairment was not reported as a relevant adverse event. The PAN study is a non-interventional study enrolling patients treated with peginterferon alfa-2a/ribavirin (PEG/RBV) with or without TLV or BOC. Here we restrict the analysis to hepatitis C virus genotype 1 patients having completed 12 (n=895) or 24 weeks (n=591) of treatment. For estimation of glomerular filtration rate (eGFR) the CKD-EPI formula was chosen. Patients on TLV 38/575 (6.6%) and BOC 10/211 (4.7%) experienced more frequently a decrease in eGFR to <60 mL/min compared to patients on PEG/RBV 1/109 (0.9%) (p<0.05). Risk factors associated with eGFR <60 mL/min in multiple logistic regression analysis were age (p<0.001), arterial hypertension (p<0.05), higher serum creatinine at baseline (p<0.001) and being on triple therapy with TLV or BOC (p<0.01). Patients with an eGFR of <60 mL/min had a lower absolute mean haemoglobin at week 12 compared to patients with an eGFR >60 mL/min (9.7 g/dL ± 1.4 g/dL versus 11.0 g/dL ± 1.7 g/dL) (p<0.001). Most patients on TLV with a decrease of eGFR <60 mL/min showed a marked improvement in renal function after discontinuation of TLV. **CONCLUSION:** Renal impairment has not been reported as safety
signal in clinical trials with TVL or BOC. However in this large cohort including patients with risk factors for renal impairment a marked decline in renal function was observed in about 5% of patients on triple therapy. In addition to being a safety concern as such, substantial ribavirin dose reductions have to be considered in these patients as anaemia was more pronounced in patients with impaired renal function. Dual treatment of chronic hepatitis C with pegylated interferon alfa and ribavirin is characterised by numerous adverse events. However renal impairment has not been identified as part of the adverse event profile. Until recently, experience with telaprevir (TLV) and boceprevir (BOC) was based exclusively on clinical trials in selected patients. In these trials renal impairment was not reported as a safety issue (1,2,3,4). However, in the French early access program cases of renal failure were observed (5). In the present study we analyzed the development of estimated glomerular filtration rate in patients treated with interferon based therapies with or without the addition of boceprevir or telaprevir in a large cohort of patients enrolled in a non-interventional study.

**Basic and Applied Science, Pre-Clinical Studies**


Efforts to treat HCV patients are focused on developing antiviral combinations that lead to the eradication of infection. Thus, it is important to identify optimal combinations from the various viral inhibitor classes. Based on viral dynamic models, HCV entry inhibitors are predicted to reduce viral load in a monophasic manner reflecting the slow death rate of infected hepatocytes (t1/2=2-70 days) and the protection of naïve, un-infected cells from HCV infection. In contrast, replication inhibitors are predicted to reduce viral load in a biphasic manner. The initial rapid reduction phase is due to the inhibition of virus production and elimination of plasma virus (t1/2~3 hours). The second, slower reduction phase results from the elimination of infected hepatocytes. Here we sought to compare the ability of HCV entry and replication inhibitors as well as combinations thereof to reduce HCV infection in persistently-infected Huh7 cells.

Treatment with 5×EC50 of entry inhibitors anti-CD81 Ab or EI-1 resulted in modest (≤1 log10 RNA copies/ml), monophasic declines in viral levels during 3 weeks of treatment. In contrast, treatment with 5×EC50 of the replication inhibitors BILN-2016 or BMS-790052 reduced extracellular virus levels more potently (~2 log10 RNA copies/ml) over time in a biphasic manner. However, this was followed by a slow rise to steady-state virus levels due to the emergence of resistance mutations. Combining an entry inhibitor with a replication inhibitor did not substantially enhance the rate of virus reduction. However, entry/repliation inhibitor and replication/repliation inhibitor combinations reduced viral levels further than monotherapies (up to 3 log10 RNA copies/ml) and prolonged this reduction relative to monotherapies. Our results demonstrated that HCV entry inhibitors combined with replication inhibitors can prolong antiviral suppression, likely due to the delay of viral resistance emergence.

It has been reported that monoclonal antibodies (MAbs) to the E1E2 glycoproteins may have the potential to prevent hepatitis C virus (HCV) infection. The protective epitopes targeted by these MAbs have been mapped to the regions encompassing amino acids 313-327 and 432-443. In this study, we synthesized these two peptides and tested the reactivity of serum samples from 336 patients, 210 of which were from Chronic Hepatitis C (CHC) patients infected with diverse HCV genotypes. The remaining 126 samples were isolated from patients who had spontaneously cleared HCV infection. In the chronic HCV-infected group (CHC group), the prevalence of human serum antibodies reactive to epitopes 313-327 and 432-443 was 24.29% (51 of 210) and 4.76% (10 of 210), respectively. In the spontaneous clearance group (SC group), the prevalence was 0.79% (1 of 126) and 12.70% (16 of 126), respectively. The positive serum samples that contained antibodies reactive to epitope 313-327 neutralized HCV pseudoparticles (HCVpp) bearing the envelope glycoproteins of genotypes 1a or 1b and/or 4, but genotypes 2a, 3a, 5 and 6 were not neutralized. The neutralizing activity of these serum samples could not be inhibited by peptide 313-327. Six samples (SC17, SC38, SC86, SC92, CHC75 and CHC198) containing antibodies reactive to epitope 432-443 had cross-genotype neutralizing activities. The neutralizing activity of sample SC38, SC86, SC92 and CHC75 was partially inhibited by peptide 432-443. However, the neutralizing activity of sample SC17 for genotype 4 HCVpp and sample CHC198 for genotype 1b HCVpp were not inhibited by the peptide. This study identifies the neutralizing ability of endogenous anti-HCV antibodies and warrants the exploration of antibodies reactive to epitope 432-443 as sources for future antibody therapies.


Dysfunctional hepatitis C virus (HCV) specific CD4(+) T cells are known to contribute to inadequate adaptive immunity in chronic hepatitis C (CHC), although the underlying mechanisms remain largely undefined. In this study, OX40 ligand (OX40L) expression was investigated in 41 treatment-naïve CHC patients, 20 sustained virological responders and 36 healthy subjects. We observed that OX40L expression was significantly upregulated in peripheral monocytes in CHC patients compared with sustained virological responders and healthy subjects. OX40L upregulation correlated significantly with plasma viral load rather than serum alanine aminotransaminase levels. Furthermore, longitudinal analyses indicated that upregulated OX40L expression on monocytes is closely associated with rapid or early virological responses in patients receiving pegylated IFN-α/ribavirin treatment. In vitro, HCV core antigen strongly stimulated monocyte expression of OX40L and blockade of TLR2 signaling significantly downregulated OX40L expression. More importantly, elevated OX40L expression was also shown to be closely associated with elevation of the HCV-specific CD4(+) T-cell response and in vitro blockade of OX40L expressed on monocytes led to impaired CD4(+) T-cell function. These findings, therefore, implicate OX40L expression can be used as a marker to evaluate antiviral treatment efficacy and extend the notion that enhancement of OX40L expression could be a good way for immunotherapy in CHC patients.

Molecular simulations illuminate the role of regulatory components of the RNA polymerase from the hepatitis C virus in influencing protein structure and dynamics.
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The RNA polymerase (gene product NS5B) from the hepatitis C virus is responsible for replication of the viral genome and is a validated drug target for new therapeutic agents. NS5B has a structure resembling an open right hand (containing the fingers, palm, and thumb subdomains), a hydrophobic C-terminal region, and two magnesium ions coordinated in the palm domain. Biochemical data suggest that the magnesium ions provide structural stability and are directly involved in catalysis, while the C-terminus plays a regulatory role in NS5B function. Nevertheless, the molecular mechanisms by which these two features regulate polymerase activity remain unclear. To answer this question, we performed molecular dynamics simulations of NS5B variants with different C-terminal lengths in the presence or absence of magnesium ions to determine the impact on enzyme properties. We observed that metal binding increases both the magnitude and the degree of correlated enzyme motions. In contrast, we observed that the C-terminus restricts enzyme dynamics. Under certain conditions, our simulations revealed a fully closed conformation of NS5B that may facilitate de novo initiation of RNA replication. This knowledge is important because it fosters the development of a comprehensive description of RNA replication by NS5B and is relevant to understanding the functional properties of a broad class of related RNA polymerases such as 3D-pol from poliovirus. Ultimately, this information may also be pertinent to designing novel NS5B therapeutics.


RNA viruses, such as hepatitis C virus (HCV), have markedly error-prone replication, resulting in high rates of mutagenesis. In addition, the standard treatment includes ribavirin, a base analog that is likely to cause mutations in different regions of the HCV genome, resulting in deleterious effects on HCV itself. The N-terminal region of the core protein is reported to block interferon (IFN) signaling by interaction with the STAT1 SH2 domain, resulting in HCV resistance to IFN therapy. In this study, mutations in the HCV core protein from IFN/ribavirin treated patients were analyzed, with particular focus on the N terminal domain of the HCV core which is reported to interact with STAT1. HCV PCR positive patients enrolled in this study were either undergoing pegylated IFN/ribavirin bitherapy and had completed 12 weeks of initial treatment or were treatment naïve patients. The HCV core protein was cloned and sequenced from these patients and mutations observed in the STAT1 interacting domain of the core protein from treated patients were characterized using in silico interaction to depict the role of these mutations in disease outcomes. Our results suggest that the amino acids at positions 2, 3, 8, 16 and 23 of the HCV core protein are critical for core-STAT1 interaction and ribavirin-induced mutations at these positions interfere with the interaction, resulting in a better response of the treated patients. In conclusion, this study anticipates that HCV core residues 2, 3, 8, 16 and 23 directly interact with STAT1. We propose that IFN/ribavirin bitherapy induced mutations in the STAT1 interacting domain of the HCV core protein may be responsible for the improved therapeutic response and viral clearance, thus amino acids 1-23 of the N-terminus of the core protein are an ideal antiviral target. However, this treatment may give rise to resistant variants that are able to
escape the current therapy. We propose similar studies in responsive and non-responsive genotypes in order to gain a broader picture of this proposed mechanism of viral clearance.


**BACKGROUND:** We explored the concept of heterologous prime/boost-vaccination using two therapeutic vaccines, currently in clinical development, aiming at treating chronically infected hepatitis C virus (HCV) patients: prime with a DNA-based vaccine expressing HCV genotype-1a NS3/4A-proteins (ChronVac-C) and boost with a Modified Vaccinia Virus Ankara-vaccine expressing genotype-1b NS3/4/5B-proteins (MVATG16643). **METHODS:** Two ChronVac-C immunizations four-weeks apart were delivered intramuscularly in combination with in vivo electroporation, and subsequently 5 or 12 weeks later boosted by three weekly subcutaneous injections of MVATG16643. Two mouse strains were utilized and we evaluated quality, magnitude and functionality of the T-cells induced. **RESULTS:** DNA-prime/MVA-boost regimen induced significantly higher levels of IFNγ- or IL-2-ELISpot responses compared to each vaccine alone, independent of the time of analysis and the time-interval between vaccinations. Both CD8+ and CD4+ T-cell responses were improved and the spectrum of epitopes recognized. A significant increase in polyfunctional IFNγ/TNFα/CD107+ CD8+ T-cells was detected following ChronVacC/MVATG16643-vaccination (from 3% to 25%) and prime/boost was the only regimen that activated quadrifunctional T-cells (IFNγ/TNFα/CD107/IL-2+). In vivo functional protective capacity of DNA-prime/MVA-boost was demonstrated in a Listeria-NS3-1a challenge model. **CONCLUSION:** We provide a proof-of-concept that immunogenicity of two HCV therapeutic vaccines can be improved using their combination, which merits further clinical development.

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**HIV/HCV COINFECTION**


Our work represents the first case report of polycystic echinococcosis co-infection with HIV, hepatitis C virus (HCV), and hepatitis B virus (HBV). Structural liver alterations were found to be related to parasitic structures and necroinflammatory foci (karyopyknosis, karyorrhexis, and karyolysis), consistent with Echinococcus vogeli. Visceral adipose tissue and intrahepatic triglyceride droplets (macrovesicular and microvesicular steatosis) indicated abnormal fat anabolism, which probably resulted from both viral-induced hepatopathy and drug-related toxicity. **In summary,** our results suggest that the observed liver abnormalities reflected the coincident exposure to hepatotropic viruses and parasites causing polycystic echinococcosis and were not indicative of opportunistic relationships among these pathogens.
In HIV/hepatitis C virus co-infected patients, higher 25-hydroxyvitamin D concentrations were not related to hepatitis C virus treatment responses but were associated with ritonavir use. Branch AD, Kang M, Hollabaugh K, Wyatt CM, Chung RT, Glesby MJ. Am J Clin Nutr. 2013 Jun 5. [Epub ahead of print]

**BACKGROUND:** Among patients with hepatitis C virus (HCV) monoinfection, 25-hydroxyvitamin D [25(OH)D] concentrations are positively associated with a response to peg-interferon/ribavirin. Data on the relation between 25(OH)D concentrations and HCV treatment response in HIV-infected patients are limited. **OBJECTIVE:** The objective was to determine whether baseline 25(OH)D concentrations predict virologic response in HIV/HCV co-infected patients and to examine variables associated with 25(OH)D concentrations ≥30 ng/mL.

**DESIGN:** Data and samples of 144 HCV genotype 1, treatment-naive patients from a completed HCV treatment trial were examined in this retrospective study. Early virologic response (EVR) was defined as ≥2 log10 reduction in HCV RNA and/or HCV RNA <600 IU/mL at week 12 of peg-interferon/ribavirin treatment. Baseline 25(OH)D was measured by liquid chromatography/tandem mass spectrometry. **RESULTS:** Compared with the non-EVR control group (n = 68), the EVR group (n = 76) was younger, had fewer cirrhotics, had a higher proportion with the IL28B CC genotype, had a higher albumin concentration, and had a lower HCV viral load at baseline (P ≤ 0.05). The difference in baseline 25(OH)D concentrations between EVR and non-EVR patients was not statistically significant (median: 25 ng/mL compared with 20 ng/mL; P = 0.23). Similar results were found for sustained virologic response (SVR). In multivariable analysis, white and Hispanic race-ethnicity (OR: 6.26; 95% CI: 2.47, 15.88; P = 0.0001) and ritonavir use (OR: 2.68; 95% CI: 1.08, 6.65; P = 0.033) were associated with higher 25(OH)D concentrations (≥30 ng/mL). **CONCLUSION:** Baseline 25(OH)D concentrations did not predict EVR or SVR. Because ritonavir impairs the conversion of 25(OH)D to the active metabolite, utilization of 25(OH)D may have been impaired in subjects taking ritonavir.


**BACKGROUND:** Depression and fatigue are common in chronic hepatitis C (CHC). **OBJECTIVE:** We report clinical predictors of these conditions in patients seen in a university clinic. **METHODS:** A total of 167 CHC patients completed the Patient Health Questionnaire-9 (PHQ-9) and Fatigue Severity Scale (FSS). Major depressive disorder (MDD) suggested by PHQ-9 was confirmed by clinical interview. FSS scores ≥41 were considered clinically significant fatigue. Logistic and multiple regression models were employed for analysis. **RESULTS:** Thirty-three percent of patients had MDD and 52% had clinically significant fatigue. Sixty-one percent were HIV-infected, among whom both MDD and clinically significant fatigue were significantly less prevalent (OR = 0.47 and 0.46, respectively). MDD was least common in patients without a history of IV drug use (OR = 0.28), and highest in methadone users (OR = 3.57). Compared with methadone users, patients with no history of IV drug use and former IV drug users had less severe fatigue (coefficients = -31.0, -34.0, respectively). Lack of a history of hepatitis treatment was also associated with less severe fatigue (coefficient = -7.6). **CONCLUSION:** Our study confirms high prevalence of fatigue and depression in CHC. HIV-positivity was associated with lower rates of MDD and clinically significant fatigue, arguably
due to support systems for people living with HIV. Higher rates of depression in methadone users might be due to intrinsically higher rates of psychopathology in this group. Being on hepatitis treatment was associated with higher rates of fatigue, probably due to the adverse effects of interferon. Our findings emphasize the importance of routine screening and evaluation of depression and fatigue in CHC populations.


**BACKGROUND:** Microbial translocation has been implicated in the pathogenesis of liver fibrosis and cirrhosis. We sought to determine whether markers of microbial translocation are associated with liver disease progression during coinfection with human immunodeficiency virus (HIV) and hepatitis C virus (HCV). **METHODS:** We measured serial plasma lipopolysaccharide (LPS), endotoxin core antibody, intestinal fatty acid-binding protein (I-FABP), soluble CD14 (sCD14), interleukin 6 (IL-6), interleukin 10, and tumor necrosis factor α (TNF-α) levels over a 5-year period in 44 HIV/HCV-coinfected women, 21 of whom experienced liver disease progression and 23 were nonprogressors. **RESULTS:** While LPS levels did not differ significantly over time between progressors and nonprogressors (P = .60), progressors had significantly higher plasma levels of sCD14, a marker of monocyte activation by LPS, at the first time point measured (P = .03) and throughout the study period (P = .001); progressors also had higher IL-6 and I-FABP levels over the 5-year study period (P = .02 and .03, respectively). The associations between progression and sCD14, I-FABP, and IL-6 levels were unchanged in models controlling for HIV RNA and CD4+ T-cell count. **CONCLUSIONS:** Although LPS levels did not differ between liver disease progressors and nonprogressors, the association of sCD14, I-FABP, and IL-6 levels with liver disease progression suggests that impairment of gut epithelial integrity and consequent microbial translocation may play a role in the complex interaction of HIV and HCV pathogenesis.


Pegylated-IFN and ribavirin remains the current treatment for chronic HCV infection in patients co-infected with HIV-1, but this regimen has low efficacy rates, particularly for HCV genotype 1/4 infection, has severe side effects and is extremely costly. Therefore, accurate prediction of treatment response is urgently required. We have recently shown that the NK cell gene, KIR2DS3 and a SNP associated with the IL28B gene synergise to increase the risk of chronic infection in primary HCV mono-infected patients. Identification of SNPs associated with the IL28B gene has also proven very powerful for predicting patient response to treatment. Patients co-infected with HIV-1 are of particular concern given they respond less well to HCV treatment, have more side effects and suffer a more rapid liver disease progression. In this study, we examined both IL28B and KIR2DS3 for their ability to predict treatment response in a cohort of HIV-1/HCV co-infected patients attending two treatment centres in Europe. We found that variation in both host genetic risk factors, IL28B and KIR2DS3, was strongly associated with sustained virological response (SVR) to treatment in our co-infected cohort (n=149). The
majority of patients who achieved a rapid virological response (RVR) achieved a SVR. However, it is currently impossible to predict treatment outcome in patients who fail to achieve an RVR. In our cohort, the presence of host genetic risk factors, IL28B-T and KIR2DS3 alleles, resulted in increased odds of treatment failure in these RVR negative patients (n=88). Our data suggests that testing for host genetic factors will improve predicting treatment responsiveness in the clinical management of co-infected patients, and provides further evidence of the importance of the innate immune system in the immune response to HCV.


**BACKGROUND:** Rates of sustained virological response (SVR) to peginterferon-ribavirin are low in patients with hepatitis C virus (HCV) genotype 1 and HIV. We aimed to assess efficacy and safety of triple therapy with boceprevir plus pegylated interferon alfa-2b (peginterferon) and ribavirin, which increases rates of SVR in patients with HCV alone. **METHODS:** In our double-blind, randomised controlled phase 2 trial, we enrolled adults (18-65 years) with untreated HCV genotype 1 infection and controlled HIV (HIV RNA <50 copies per mL) at 30 academic and non-academic study sites. We randomly allocated patients (1:2) according to a computer generated sequence, stratified by Metavir score and baseline HCV RNA level, to receive peginterferon 1·5 μg/kg per week with weight-based ribavirin (600-1400 mg per day) for 4 weeks, followed by peginterferon-ribavirin plus either placebo (control group) or 800 mg boceprevir three times per day (boceprevir group) for 44 weeks. Non-nucleoside reverse-transcriptase inhibitors, zidovudine, and didanosine were not permitted. The primary efficacy endpoint was SVR (defined as undetectable plasma HCV RNA) at follow-up week 24 after end of treatment. We assessed efficacy and safety in all patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT00959699.

**FINDINGS:** From Jan 15, 2010, to Dec 29, 2010, we enrolled 99 patients, 98 of whom received at least one treatment dose. 40 (63%) of 64 patients in the boceprevir group had an SVR at follow-up week 24, compared with ten (29%) of 34 control patients (difference 33·1%, 95% CI 13·7-52·5; p=0·0008). Adverse events were more common in patients who received boceprevir than in control patients: 26 (41%) versus nine (26%) had anaemia, 23 (36%) versus seven (21%) pyrexia, 22 (34%) versus six (18%) decreased appetite, 18 (28%) versus five (15%) dysgeusia, 18 (28%) versus five (15%) vomiting, and 12 (19%) versus two (6%) neutropenia. Three patients who received boceprevir plus peginterferon-ribavirin and four controls had HIV virological breakthrough. **INTERPRETATION:** Boceprevir in combination with peginterferon-ribavirin could be an important therapeutic option for patients with HCV and HIV.


**OBJECTIVE:** We hypothesized that, in Human Immunodeficiency Virus and Hepatitis C Virus (HIV/HCV) co-infected patients who did not respond to peg-interferon and ribavirin, a maintenance therapy with peg-interferon could induce fibrosis regression. **METHODS:** This
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was a randomized study with two parallel groups. HIV/HCV co-infected patients received peg-interferon α-2a at 180 μg/week or remained on observation for 96 weeks. The primary endpoint was the percentage of patients who experienced a decrease of at least one point in their Metavir fibrosis score between initial and final liver biopsies. Secondary endpoints included plasma fibrosis markers at week 96, occurrence of HCV-related complications, and survival.

RESULTS: A total of 52 patients were randomized (peg-interferon: 25; control: 27) including 18 with cirrhosis. The median (interquartile range) age was 44 (40-46) years, and 69% were male. A total of 64% had ALT levels >1.5 normal values, and the CD4 cell count was 391 (296-537) cells/mm3; 67% of patients had HIV RNA <200 copies/mL at entry. The main endpoint was assessed in 41 patients. Response rates were 3/20 (15%) and 4/21 (19%) in the peg-interferon and control groups, respectively (p = 0.99). There was no significant difference between peg-interferon and control groups on plasma fibrosis markers at the final visit. Severe liver-related complications were observed in 2 and 5 patients in peg-interferon and control groups, respectively. Three deaths were observed, all in the control group. CONCLUSIONS: A maintenance therapy with peg-interferon α-2a over 96 weeks in HIV/HCV co-infected patients, who were non-responders to HCV treatment, did not change liver fibrosis.


OBJECTIVE: To assess the ability of the cirrhosis risk score (CRS) to predict liver fibrosis progression in HIV/HCV coinfected patients. DESIGN: Retrospective follow-up study. METHODS: Based on a minimum follow-up time of 10 years with HCV infection, 190 HIV/HCV coinfected patients were classified according to their METAVIR score: i) 25 non-progressor patients who did not develop fibrosis (F0); and ii) 165 progressor patients who developed fibrosis (F≥1). Seven polymorphisms of CRS signature and IL28B genotype were performed using the GoldenGate® assay. The CRS signature was calculated by Naïve Bayes formula as previously described. RESULTS: Non-progressors had CRS values significantly lower than progressors (0.61 versus 0.67; p=0.043). Among the progressors, we observed similar CRS values through all the fibrosis stages (F1/F2/F3/F4). The percentage of patients with CRS>0.70 (high-risk of developing fibrosis) was higher in progressors than in non-progressors; but the percentages with values between 0.50-0.70 (intermediate risk) and <0.50 (low risk) were quite similar for each of the fibrosis stages (p=0.047). The area under the receiver operating characteristic curve (AUROC) of CRS for discriminating non-progressor versus progressor was 0.625 (p=0.043). When clinical variables were considered (age at HCV infection, IDU, gender, IL28B and HCV genotype), the AUROC of CRS improved up to 0.739 (p<0.001). CONCLUSION: CRS itself seems not to be a good marker for identifying


Hepatitis C virus (HCV) infection is frequent among HIV-infected patients. We describe, the characteristics of 6 HIV/HCV-coinfected patients with B-cell non-Hodgkin lymphoma (NHL) included in a prospective cohort study of HIV-related lymphomas. Five of the 6 cases had
features of marginal zone/lymphoplasmacytic NHL versus 1 of 33 HIV only-infected patients. Remarkably, anti-HCV treatment led to a hematological response in a patient with splenic marginal zone lymphoma. This supports the role of chronic antigenic stimulation by HCV on lymphomagenesis and further evaluation of HCV antiviral therapy in coinfected patients with NHL.


One-third of all HIV-infected individuals in the United States are estimated to be coinfected with the hepatitis C virus (HCV). Treatment of chronic hepatitis C in patients coinfected with HIV is a complex problem associated with toxicities and drug interactions between HIV antiretrovirals and interferon and ribavirin. In recent HCV treatment studies, we observed a previously unreported development of hypophosphatemia in HIV/HCV-coinfected patients treated with interferon/ribavirin (IFN/RBV). To further investigate this observation, we retrospectively reviewed 61 HIV/HCV-coinfected patients on antiretrovirals (ARVs) during treatment with IFN/RBV as well as 154 HIV-infected patients treated with ARVs alone. We found that HIV/HCV-coinfected patients on IFN/RBV therapy were more likely to develop frequent (57% vs. 13%, IFN/RBV-treated patients vs. no IFN/RBV; \( \chi^2=0.001 \)) and higher-grade hypophosphatemia (67.0% Grade 2, 33.3% Grade 3 vs. 94.7% Grade 2, 5.3% Grade 3, IFN/RBV-treated patients vs. no IFN/RBV; \( \chi^2<0.001 \)) than untreated patients. In addition, we found that the new onset of hypophosphatemia after IFN/RBV treatment initiation was followed by a diminished frequency of this toxicity upon cessation of IFN/RBV, supporting the idea that a drug-drug interaction may increase the risk of this toxicity. To understand the risks of developing this toxicity, we evaluated the association between individual ARV use and hypophosphatemia incidence. Our data suggest that concomitant tenofovir (TDF) use may be a risk factor for the development of hypophosphatemia in HIV/HCV-coinfected patients treated with IFN/RBV. Although the etiology of this abnormality is likely multifactorial, clinicians should be aware of hypophosphatemia as a potential marker of renal toxicity in HIV/HCV-coinfected patients being treated with IFN/RBV regimens.

**Epidemiology, Diagnostics, and Miscellaneous Works**


**DESCRIPTION:** Update of the 2004 U.S. Preventive Services Task Force (USPSTF) recommendation on screening for and treatment of hepatitis C virus (HCV) infection in asymptomatic adults. **METHODS:** The Agency for Healthcare Research and Quality commissioned 2 systematic reviews on screening for and treatment of HCV infection in asymptomatic adults, focusing on evidence gaps identified in the previous USPSTF recommendation and new studies published since 2004. The evidence on screening for HCV in pregnant women was also considered. **POPULATION:** This recommendation applies to all
asymptomatic adults without known liver disease or functional abnormalities.

**RECOMMENDATION:** The USPSTF recommends screening for HCV infection in persons at high risk for infection. The USPSTF also recommends offering 1-time screening for HCV infection to adults born between 1945 and 1965. (B recommendation).


**OBJECTIVE:** The aim of this study was to explore the feasibility and the efficacy of a physiotherapy-led exercise program in changing the health status of a sample of patients with chronic hepatitis C. **DESIGN:** A single-blind randomized controlled trial was conducted in a sample of patients with iatrogenically acquired hepatitis C in Ireland. Twenty-two participants were recruited and randomly assigned to exercise (n = 10) and control (n = 12) groups. Both groups received a generic exercise advice leaflet, and the exercise group attended 12 exercise sessions for 6 wks. A battery of physical performance measures and patient-reported outcome measures were assessed at baseline and 6 wks, with 1-yr follow-up of the self-reported measures. **RESULTS:** Significant group by time interactions during the 6-wk period were found for pain (F(1,20) = 5.15, P = 0.034), grip strength (F(1,20) = 5.94, P = 0.024), aerobic capacity (F(1,20) = 5.73, P = 0.024), and depression (F(1,20) = 6.16, P = 0.022), with the exercise group showing greater positive change. The exercise group also had superior gains in the 36-Item Short-Form Health Survey vitality and social function scores (P < 0.05). The short-term gains were not sustained at 1 yr. **CONCLUSIONS:** This pilot study shows the feasibility of exercise in hepatitis C management, improving physical fitness, psychologic function, and quality-of-life without worsening symptoms in the short term.


San Diego, California shares the world's busiest land border crossing with Tijuana, Mexico—a city where 95 % of injection drug users (IDUs) test hepatitis C virus (HCV) antibody-positive. Yet, little is known about the prevalence and risk behaviors for HCV among IDUs in San Diego. In 2009-2010, 18-40-year-old IDUs in San Diego County completed a risk assessment interview and serologic testing for HCV and HIV infection. Recruitment involved respondent-driven sampling, venue-based sampling at a syringe exchange program, and convenience sampling. Correlates of HCV infection were identified by multivariable logistic regression. Among 510 current IDUs, 26.9 % (95 % CI 23.0-30.7 %) and 4.2 % (95 % CI 2.4-5.9 %) had been infected with HCV and HIV, respectively. Overall, median age was 28 years; 74 % were male; 60 % white and 29 % Hispanic; and 96 % were born in the U.S. Median years of injecting was 6; 41 % injected daily; 60 % injected heroin most often; 49 % receptively shared syringes and 68 % shared other injection paraphernalia; and only 22 % reported always using new syringes in the past 3 months. Two thirds had ever traveled to Mexico and 19 % injected in Mexico. HCV infection was independently associated with sharing injection paraphernalia (adjusted odds ratio [AOR] = 1.69) and SEP use (AOR = 2.17) in the previous 3 months, lifetime history of drug overdose (AOR = 2.66), and increased years of injecting (AOR = 2.82, all P values <0.05). Controlling for recruitment method did not alter results. HCV infection prevalence among IDUs

Patients infected with chronic hepatitis C virus (HCV) commonly suffer from the triad of depression, pain and fatigue. This symptom triad in HCV is likely influenced by additional psychological and interpersonal factors, although the relationship is not clearly understood. This retrospective study aimed to characterize the relationship between attachment style and depressive and physical symptoms in the HCV-infected population. Over 18 months, 99 consecutively referred HCV infected patients were assessed with the Hamilton Depression Rating Scale (HDRS), Fatigue Severity Scale, Patient Health Questionnaire-15 for physical symptoms and the Relationship Questionnaire for attachment style. An ANOVA was used to identify differences between attachment styles and Pearson correlations were used to evaluate the association between depression, fatigue and physical symptoms. Approximately 15% of patients in the sample had a fearful attachment style. Patients with fearful attachment style had significantly higher depressive symptoms compared to a secure attachment style (p = .025). No differences in physical and fatigue symptoms were observed between attachment styles. Further, HDRS scores were significantly associated with fatigue scores (p < .001) and physical symptoms (p < .001), reinforcing the relationship between these symptom domains in HCV-infected patients. Although depressive, physical and fatigue symptoms are inter-related in HCV-infected patients, our study results suggest that only depressive symptoms were influenced by the extremes of attachment style. Screening of relationship styles may identify at-risk HCV-infected individuals for depression who may have difficulty engaging in care and managing physical symptoms.


Although injection drug use (IDU) and blood transfusions prior to 1992 are well-accepted risk factors for hepatitis C virus (HCV) infection, many studies that evaluated tattooing as a risk factor for HCV infection did not control for a history of IDU or transfusion prior to 1992. In this large, multicenter, case-control study, we analyzed demographic and HCV risk factor exposure history data from 3,871 patients, including 1,930 with chronic HCV infection (HCV RNA-positive) and 1,941 HCV-negative (HCV antibody-negative) controls. Crude and fully adjusted odds ratios (ORs) of tattoo exposure by multivariate logistic regression in HCV-infected versus controls were determined. As expected, IDU (65.9% versus 17.8%; P < 0.001), blood transfusion prior to 1992 (22.3% versus 11.1%; P < 0.001), and history of having one or more tattoos (OR, 3.81; 95% CI, 3.23-4.49; P < 0.001) were more common in HCV-infected patients than in control subjects. After excluding all patients with a history of ever injecting drugs and those who had a blood transfusion prior to 1992, a total of 1,886 subjects remained for analysis (465 HCV-positive patients and 1,421 controls). Among these individuals without traditional risk factors, HCV-positive patients remained significantly more likely to have a history of one or more tattoos.
after adjustment for age, sex, and race/ethnicity (OR, 5.17; 95% CI, 3.75-7.11; P < 0.001).

**CONCLUSION:** Tattooing is associated with HCV infection, even among those without traditional HCV risk factors such as IDU and blood transfusion prior to 1992.


**BACKGROUND:** An estimated 1% to 1.9% of North Americans are infected with the hepatitis C virus (HCV). Although Indigenous peoples are considered to bear the highest burden, there are only limited data regarding the demographic features and epidemiology of hepatitis C in this population. **OBJECTIVES:** To document the demographic characteristics, rates of newly diagnosed hepatitis C cases and prevalence of HCV infection in a Canadian First Nations population, and to compare the findings with an infected non-First Nations population. **METHODS:** A research database spanning 1991 to 2002 was developed, linking records from multiple clinical and administrative sources. Over a 12-year period, 671 First Nations and 4347 non-First Nations HCV-positive Canadians were identified in the province of Manitoba. Demographics, residence and time trends were compared between infected First Nations and non-First Nations persons. **RESULTS:** HCV-infected First Nations individuals were younger (mean [± SD] age 33.0±0.4 years versus 39.7±0.2 years; P<0.0001), more often female (60% versus 40%; P<0.0001) and more often resided in urban centres (73% versus 27%; P<0.001). The rate of newly diagnosed HCV cases was 2.5-fold (91.1 per 100,000 versus 36.6 per 100,000; P<0.000) and prevalence 2.4-fold (801.7 per 100,000 versus 334.8 per 100,000; P<0.000) higher among the First Nations relative to non-First Nations populations. **CONCLUSIONS:** The results of the present large population-based study indicate that the First Nations population with hepatitis C is characteristically different from infected non-First Nations persons. The results also describe higher rates of newly diagnosed cases and prevalence of HCV infection in the First Nations population. These findings should serve as an important baseline for future primary prevention and therapeutic intervention strategies in this high-risk population.


Despite the seriousness of Hepatitis C (HCV), many patients do not receive treatment. One promising means of addressing these issues for medically ill patients is through participation in support group services. This study examined individual-, treatment- and system-level factors associated with enrolling in a support group intervention (psychoeducation) for persons with HCV. A total of 235 research participants were recruited as part of a NIAAA-funded randomized clinical trial for patients with HCV and their family members, with 172 (73.2 %) agreeing to enroll in the psychoeducation trial and 63 (26.8 %) declining. Factors leading to enrollment indicated that individuals without employment, with certain personality structures (low cooperativeness and self-directedness), and traveling greater distance to their group were more likely to agree to participate. Populations being seen in public settings demonstrate a desire for additional support and education, but at the same time these potential participants are faced with challenges to following through and enrolling in the desired services.
BACKGROUND: The American Association for the Study of Liver Diseases (AASLD) practice guidelines provide recommendations in diagnosing and managing patients with liver disease from available scientific evidence in combination with expert consensus opinions.

AIM: To systematically review the evolution of recommendations from AASLD guidelines and identify gaps limiting the evidence-based foundations of these guidelines. METHODS: Initial and current AASLD guidelines published from January 1998 to August 2012 were reviewed. The AGREE II instrument was used to evaluate rigour and transparency of guideline development. The number of recommendations, distribution of grades (strength or certainty), classes (benefit versus risk) and types of recommendations were evaluated. Whenever possible, multiple versions were evaluated for evolving scientific evidence. RESULTS: A total of 991 recommendations from 28 guidelines on 17 topics were evaluated. From initial to current guidelines, the total number of recommendations increased by 36% (512 to 699). The largest increases were from chronic hepatitis B (HBV) (+71), liver transplantation (+53) and autoimmune hepatitis (AIH) (+27). Most current recommendations are grade II (44%) and less than 20% are grade I. The AGREE II evaluation showed global improvement in guideline quality. Both HBV and chronic hepatitis C guidelines had greatest increases in grade I recommendations (+383% and +67%, respectively). The greatest increases in treatment recommendations were from HBV (grade I, +1150%), liver transplantation (grade II, +112%) and AIH (grade III, +105%).

CONCLUSIONS: Despite significant increases in the numbers of recommendations within AASLD practice guidelines over time, only a minority are supported by grade I evidence, highlighting the need for developing well-designed investigations to provide evidence for areas of uncertainty and improving the quality of future guidelines in hepatobiliary diseases.


Individual epidemiologic studies as well as the pooled analysis of observational studies have indicated the association between type 2 diabetes (T2D) and hepatitis C virus infection (HCV). Whether HCV infection is the cause of diabetes or diabetic patients are more prone to get HCV infection is still in question. The objective of the present review was to provide answers to this issue, based on available evidence from epidemiologic, molecular, experimental and therapeutic studies. Our current understanding of how chronic HCV infection could induce T2D is incomplete, but it seems twofold based on both direct and indirect roles of the virus. HCV may directly induce insulin resistance (IR) through its proteins. HCV core protein was shown to stimulate suppressor of cytokine signaling, resulting in ubiquitination and degradation of tyrosine kinase phosphorylated insulin receptor substrates (IRS1/2) in proteasomes. HCV-nonstructural protein could increase protein phosphatase 2A which has been shown to inactivate the key enzyme Akt by dephosphorylating it. Insulin signaling defects in hepatic IRS-1 tyrosine phosphorylation and PI3-kinase association/activation may contribute to IR, which leads to the development of T2D in patients with HCV infection. The peroxisome proliferator-activated receptors (PPARs) are also implicated. PPARα/γ, together with their obligate partner RXR, are the main nuclear receptors expressed in the liver. PPARα upregulates glycerol-3-phosphate...
dehydrogenase, glycerol kinase, and glycerol transport proteins, which allows for glucose synthesis during fasting states. Decreased activity of PPARs could attribute to HCV-induced IR. Immune-mediated mechanisms may be involved in the indirect role of HCV in inducing IR. It is speculated that TNF-alpha plays a major role in the pathogenesis of IR through lowering IRS1/2. Furthermore, HCV infection-triggered ER stress could lead to the activation of PP2A, which inhibits both Akt and the AMP-activated kinase, the regulators of gluconeogenesis. In summary, we illustrate that HCV infection is accompanied by multiple defects in the upstream insulin signaling pathway in the liver that may contribute to the observed prevalence of IR and diabetes. Future studies are needed to resolve this issue.


BACKGROUND: Illicit drug users have a high prevalence of HCV and represent the majority of newly infected persons in the U.S. Despite the availability of effective HCV treatment, few drug users have been evaluated or treated for HCV. Racial and ethnic minorities have a higher incidence and prevalence of HCV and higher HCV-related mortality. Factors contributing to poor engagement in care are incompletely understood. METHODS: Fourteen mixed-gender focus groups of either African American or Latino/a drug users (N = 95) discussed barriers to HCV testing and treatment. Themes were identified through content analysis of focus group discussions. RESULTS: Many drug users were tested for HCV in settings where they were receiving care. Outside of these settings, most were unaware of voluntary test sites. After testing HCV positive, drug users reported not receiving clear messages regarding the meaning of a positive HCV test, the impact of HCV infection, or appropriate next steps including HCV clinical evaluations. Many drug users perceived treatment as unimportant because they lacked symptoms, healthcare providers minimized the severity of the diagnosis, or providers did not recommend treatment. Mistrust of the motivations of healthcare providers was cited as a barrier to pursuing treatment. Social networks or social interactions were a source of HCV-related information and were influential in shaping drug users perceptions of treatment and its utility. CONCLUSION: Drug users perceived a paucity of settings for self-initiated HCV testing and poor provider-patient communication at test sites and during medical encounters. Notably, drug users reported having an unclear understanding about the meaning of a positive HCV test, the health implications of HCV infection, the importance of clinical evaluations and monitoring, and of treatment options for HCV. Efforts to improve the delivery of clinical messages about HCV infection for drug users at test settings and clinical encounters are needed.


BACKGROUND: Recent guidelines recommend testing all individuals born during 1945-1965 for hepatitis C virus (HCV) antibody. For antibody-positive patients, subsequent RNA testing is necessary to determine current infection status. This study aimed to assess whether clinicians order HCV RNA tests as recommended for antibody-positive patients and to identify barriers to such testing. METHODS: We sampled individuals newly reported to the New York City Department of Health and Mental Hygiene's HCV surveillance system and collected information
from clinicians. For patients without RNA test results, we asked the reason an RNA test was not ordered and requested that the clinician order the test. **RESULTS:** Of 245 antibody-positive patients, 67% were tested for HCV RNA (for 21% of these, the test was ordered only after our request); 33% had no RNA testing despite our request. Patients without RNA testing were seen in medical facilities (47%), detox facilities (30%), and jail/prison (15%). Reasons RNA testing was not done were that the patient did not return for follow-up (35%), the facility does not do RNA testing (22%), and the patient was tested in jail (15%). **CONCLUSIONS:** In our study, one third of patients did not get complete testing for accurate diagnosis of HCV, which is essential for medical management. Additional education for clinicians about the importance of RNA testing may help. However, with improved antiviral treatments now available for HCV, it is time for reflex HCV RNA testing for positive antibody tests to become routine, just as reflex Western blot testing is standard for human immunodeficiency virus.


**OBJECTIVE:** Much of the research to date on barriers to treatment for patients with hepatitis C has approached the problem from either the perspective of the medical provider or the healthcare system. **METHODS:** To better understand these barriers from the patients’ perspectives, nine exploratory focus groups of patients with hepatitis C (N=48) were conducted in 2008 and 2009, using a hybrid qualitative analysis. **RESULTS:** Eight content categories emerged. Treatment-related issues, including barriers to care, were most emphasized, representing nearly one-half of the entire content. Need for accurate disease-related information was also extensively discussed. Social factors were important, including considerable focus on stigma. Participants described coping abilities including faith and perseverance. **CONCLUSION:** Areas of concern expressed in these focus groups represent underexplored areas that may warrant additional attention or areas for intervention and investigation, such as exploring differences between perceptions of patients and providers regarding the hepatitis C treatment process and addressing barriers to care.

**Liver Cancer**


**OBJECTIVE:** The objective of our study was to describe the cross-sectional imaging appearance of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C virus (HCV) infection in the absence of advanced fibrosis and cirrhosis. **MATERIALS AND METHODS:** This study is a retrospective review of our surgical database to identify patients with chronic HCV infection and HCC who underwent hepatectomy and who had undergone preoperative CT or MRI. Only patients with a Metavir fibrosis score of F0, F1, or F2 on pathology were included. Patients with hepatitis B virus coinfection or other causes of chronic liver disease and patients with histopathologic evidence of advanced fibrosis or cirrhosis (Metavir scores F3 and F4) were excluded. Contrast-enhanced CT or MRI examinations performed within 2 months before surgery were reviewed for the number, size, and location of tumors; tumor enhancement characteristics; and presence of macrovascular invasion. **RESULTS:** Two hundred forty-five
resections of HCC in patients with HCV were performed in our institution from 1987 to 2012. Of this group, 26 patients (10.6%) had a Metavir fibrosis score of F0, F1, or F2; of those patients, 19 (18 men and one woman; 18 non-Asian patients and one Asian patient; mean age, 64 years) had imaging studies available for review. Twenty-one HCCs (mean size, 4.5 cm; range, 0.9-14.8 cm) were evaluated at imaging. Typical wash-in and washout characteristics were seen in 16 of 19 viable lesions (84.2%). The remaining two HCCs were completely necrotic after transarterial chemoembolization. Eighteen patients had a solitary tumor. Most tumors (15/21, 71.4%) developed in the right hepatic lobe. **CONCLUSION:** HCC can develop in patients with chronic HCV without advanced fibrosis or cirrhosis, most frequently in older non-Asian men, and usually appears as a large solitary tumor with a typical wash-in-washout enhancement pattern.

The role of growth factors produced by the liver, including insulin-like growth factor-1 (IGF-1) and its main binding protein, IGF binding protein-3 (IGFBP-3), in hepatitis C virus (HCV)-associated carcinogenesis has only partially been recognized and there is not much data available on the local expression of IGF-1 and IGFBP-3 in chronic hepatitis C (CH C). Therefore, the aim of the present study was to evaluate the IGF 1 and IGFBP 3 serum levels and tissue expression in liver biopsies of CH C patients (n=37) and hepatocellular carcinoma (HCC) samples (n=61) as related to age- and gender-matched control serum samples (n=15) and healthy liver samples (n=10). Serum concentrations of IGF-1 (S-IGF-1) and IGFBP 3 (S-IGFBP 3) were measured by the ELISA method. Tissue expression of proteins was detected using ABC immunocytochemistry and evaluated applying a spatial visualization technique. Concentrations of S-IGF-1 and hepatic expression of IGF-1 (H-IGF-1) proved to be lower in CH C compared to the controls. No significant differences were detected in the concentration of S-IGFBP-3 between the studied groups but the S-IGF-1/IGFBP-3 ratio in the CH C group was significantly lower compared to the control. H-IGFBP-3 was higher in CH C compared to those in the control and HCC. In HCC, lower expression of H-IGF-1 was detected compared to the control and a higher H-IGF-1/IGFBP-3 ratio compared to CH-C. A negative correlation was detected between S-IGF-1 and S-IGF-1/IGFBP-3 ratio, on the one hand, and age, grading and concentration of α-fetoprotein (AFP) on the other, while H-IGFBP-3 was negatively correlated with BMI in the CH C group. In patients with CH C, the H IGF 1/IGFBP 3 ratio was higher compared to that of the S IGF 1/IGFBP 3 ratio. The studies documented a disturbed H IGF 1 and H IGFBP 3 in CH C, which may be of significance in carcinogenesis. Examination of serum concentration and tissue expression of the two proteins and, first of all, estimation of the IGF 1/IGFBP 3 ratio may provide additional (to the estimation of IGF 1 and AFP) non-invasive markers in HCV related liver injury.

**OBJECTIVE AND BACKGROUND:** Although p21 ras has been reported to be upregulated in hepatocellular carcinoma complicating chronic hepatitis C type I, p21 ras has a different role...
in advanced stages, as it has been found to be downregulated. The goal of this study was to investigate the status of p21 ras in early-stage/low-grade and late-stage/high-grade hepatocellular carcinoma and its possible link to apoptosis. **MATERIAL AND METHODS:** Thirty-five cases each of chronic HCV hepatitis type 4 (group I) and cirrhosis with hepatocellular carcinoma (HCC) complicating chronic HCV hepatitis (groups II and III) were immunohistochemically evaluated using a p21 ras polyclonal antibody. The apoptotic index was determined in histologic sections using the terminal deoxynucleotidyl transferase-mediated d-UTP biotin nick end labeling (TUNEL) assay. **RESULTS:** Significant differences (P=0.001) were detected in p21 ras protein expression between the three groups. A near 2-fold increase in p21 ras staining was observed in the cirrhotic cases compared to the hepatitis cases, and p21 ras expression was decreased in the HCC group. p21 ras expression correlated with stage (r=0.64, P=0.001) and grade (r=(-)0.65, P=0.001) in the HCC group and grade in the HCV group (r=0.44, P=0.008). Both p21 ras expression and TUNEL-LI were significantly lower in large HCCs compared to small HCCs (P=0.01 each). The TUNEL values were negatively correlated with stage in the HCC group (r=(-)0.85, P=0.001). The TUNEL values were also negatively correlated with grade in both the HCV and HCC groups (r=0.89, P=0.001 and r=(-)0.53, P=0.001, respectively). The p21 ras scores were significantly correlated with the TUNEL-LI values in the HCC group (r=0.63, P=0.001) and HCV group (r=0.88, P=0.001). **CONCLUSIONS:** p21 ras acts as an initiator in HCC complicating type 4 chronic HCV and is downregulated with HCC progression, which most likely promotes tumor cell survival because it facilitates the downregulation of apoptosis with tumor progression.


**BACKGROUND:** Guidelines recommend screening for hepatocellular cancer (HCC) with ultrasonography. The performance of ultrasonography varies widely. Computed tomography (CT) is less operator dependent. **AIM:** To compare the performance and cost of twice-a-year ultrasonography to once-a-year triple-phase-contrast CT for HCC screening in veterans. We hypothesised that CT detects smaller HCCs at lower overall cost. **METHOD:** One hundred and sixty-three subjects with compensated cirrhosis were randomised to biannual ultrasonography or yearly CT. Twice-a-year alpha-feto protein testing was performed in all patients. Contingency table analysis using chi-squared tests was used to determine differences in sensitivity and specificity of screening arms, survival analysis with Kaplan-Meier method to determine cumulative cancer rates. Multivariate logistic regression models were used to examine predictive factors. **RESULTS:** Hepatocellular cancer incidence rate was 6.6% per year. Nine HCCs were detected by ultrasonography and eight by CT. Sensitivity and specificity were 71.4% and 97.5%, respectively, for ultrasonography vs. 66.7% and 94.4%, respectively, for CT. Although 58.8% of screen-detected HCC were early stage (Barcelona Clinic Liver Cancer stage A), only 23.5% received potentially curative treatment despite all treatment options being available. HCC-related and overall mortality were 70.5% and 82.3%, respectively, in patients with screen-detected tumour. Overall costs were less for biannual ultrasonography than annual CT. **CONCLUSIONS:** Biannual ultrasonography was marginally more sensitive and less costly for detection of early HCC compared with annual CT.
Despite early detection, HCC-related mortality was high. These data support the use of biannual ultrasonography for HCC surveillance in a US patient population (NCT01350167).


Hepatocellular carcinoma (HCC) is a major cause of cancer death worldwide, accounting for over half a million deaths per year. The geographic pattern of HCC incidence is parallel to exposure to viral etiologic factors. Its incidence is increasing, ranging between 3% and 9% annually depending on the geographical location, and variability in the incidence rates correspond closely to the prevalence and pattern of the primary etiologic factors. Chronic infections with hepatitis B viruses or hepatitis C viruses have both been recognized as human liver carcinogens with a combined attributable fraction of at least 75% of all HCC cases. Multiple non-viral factors have been implicated in the development of HCC. Increased body mass index and diabetes with subsequent development of non-alcoholic steatohepatitis represent significant risk factors for HCC. Other non-viral causes of HCC include iron overload syndromes, alcohol use, tobacco, oral contraceptive, aflatoxin, pesticides exposure and betel quid chewing, a prevalent habit in the developing world. Wilson disease, α-1 antitrypsin deficiency, Porphyrias, autoimmune hepatitis, Schistosoma japonicum associated with positive hepatitis B surface antigen, and thorotrast-ray are also contributing hepatocellular carcinoma. In addition, primary biliary cirrhosis, congestive liver disease and family history of liver cancer increase the risk of HCC incident. **In conclusion,** clarification of relevant non-viral causes of HCC will help to focus clinicians on those risk factors that are modifiable. The multilevel preventative approach will hopefully lead to a reduction in incidence of non-viral HCC, and a decrease in the patient morbidity and mortality as well as the societal economic burden associated with HCC.


**OBJECTIVE AND BACKGROUND:** The roles of chronic hepatitis B virus (HBV) co-infection (CI) in carcinogenesis of hepatitis C virus (HCV)-associated hepatocellular carcinoma (HCC) remained controversial. To gain new insights into this issue, we investigated the postoperative prognostic value of HBVCI in HCV-associated HCC. **METHODS:** A study cohort of 115 liver tissues obtained from the noncancerous parts of surgically removed HCV-associated HCCs were subjected to virological analysis in a tertiary care setting. Assayed factors included clinicopathological variables, tissue amounts of viral genomes, genotypic characterization of viruses, as well as the presence of overt (serum HBsAg positive) or occult (serum HBsAg negative but tissue HBV-DNA positive) HBVCI. Cox proportional hazard model was used to estimate postoperative survivals. **RESULTS:** Of the 115 patients, overt and occult HBVCIs were detected in 35 and 16 patients, respectively. Multivariate analysis revealed that tumor size >3 cm (adjusted hazard ratio (AHR), 2.079 [95% confidence interval, 1.149∼3.761]), alpha-fetoprotein >8 ng/mL (AHR, 5.976 [2.007∼17.794]) albumin <4 g/dL(AHR, 2.539 [1.399∼4.606]), ALT >50 U/L (AHR,1.086 [1.006∼1.172]), presence of occult HBVCI (AHR, 2.708 [1.317∼5.566]), and absence of overt HBVCI (AHR, 2.216 [1.15∼4.269]) were independently associated with unfavorable disease-free survival. Patients with occult HBVCI had a shorter disease-free...
(P=0.002), a shorter overall survival (P=0.026), a higher bilirubin level (P=0.003) and a higher prevalence of precore G1896A mutation (P=0.006) compared with those with overt HBVCI. 

**CONCLUSION:** Occult and overt HBVCI served as independent predictors for postoperative survival in HCV-associated HCC.


Hepatocellular carcinoma (HCC) is one of the most deadly cancers. Aberrant oncogenic activation of the Wnt/β-catenin signaling pathway contributes to hepatocellular carcinogenesis. Various epigenetic modifications of the Wnt antagonist secreted frizzled-related protein (SFRP) family have been implicated in regulating Wnt signaling. Here, we report that Hepatitis C virus (HCV) core protein downregulates SFRP1 expression when it is expressed in Huh7 and HepG2 cells. SFRP1 expression can be effectively restored by using either a DNA methylation inhibitor alone or in combination with a histone deacetylase inhibitor. DNA methylation analysis of the SFRP1 promoter revealed that cytosine-phosphate-guanine (CpG) islands close to the transcriptional start site (TSS) in the SFRP1 promoter were hypermethylated in core-expressing Huh7 cells, suggesting that HCV core protein may downregulate SFRP1 expression by inducing hypermethylation of the SFRP1 promoter. Chromatin immunoprecipitation revealed that HCV core protein markedly increased the expression level and binding of DNA methyltransferase-1 (Dnmt1) and histone deacetylase-1 (HDAC1) to the TSS of the SFRP1 promoter region, resulting in repression of acetyl-histone H3-binding capacity to SFRP1 promoter and the eventual epigenetic silencing of SFRP1 expression. Furthermore, the core protein-promoted cell proliferation, migration and invasiveness were effectively abrogated either by Dnmt1 knockdown or restoration of SFRP1 expression in hepatoma cells. Dnmt1 knockdown or SFRP1 overexpression also inhibited HCV core-induced epithelial-mesenchymal transition (EMT) and significantly decreased the expression levels of activated β-catenin and Wnt/β-catenin target genes, c-Myc and cyclin D1. We further showed that knockdown of Dnmt1 and restoration of SFRP1 inhibited core-induced in vivo tumor growth and aggressiveness in a xenograft HCC model. Taken together, our results strongly suggest that the HCV core-induced epigenetic silencing of SFRP1 may lead to the activation of the Wnt signaling pathway and thus contribute to HCC aggressiveness through induction of EMT.


**BACKGROUND:** Although cirrhosis is common among Western hepatocellular carcinoma (HCC) patients, a substantial proportion are not cirrhotic. Studies examining surgical outcomes in noncirrhotic patients primarily evaluate Asian populations and liver resections. We describe cirrhotic and noncirrhotic HCC patients undergoing resection and transplantation at a Western institution. **METHODS:** We retrospectively reviewed 188 HCC patients treated surgically from 2000 to 2011 at a single Western institution. The primary endpoint was recurrence. Secondary endpoints included time to recurrence and overall survival. **RESULTS:** We evaluated 138 cirrhotic and 50 noncirrhotic patients with a median follow-up of 33.8 months. Noncirrhotics mostly underwent liver resection (90%), whereas cirrhotics primarily underwent transplantation.
Hepatitis B was the most common underlying liver disease for noncirrhotics (64%), whereas hepatitis C (55%) and alcohol abuse (32%) predominated among cirrhotics. Pathologic evaluation demonstrated tumors in noncirrhotics that were fewer in number, larger, less differentiated, and more likely to have vascular invasion. Recurrence was more common for noncirrhotics (36 vs 18%; P = .008) and more common after resection compared with transplantation. Overall median survival was 46.9 months for both groups. After resection, noncirrhotics had longer survival times than did cirrhotics (41.6 vs 32.9 months; P = .04). Vascular invasion was an independent predictor for recurrence; tumor size was a predictor of mortality. CONCLUSION: Noncirrhotics in our Western cohort had higher risk pathologic features, more frequently underwent resection, and suffered more recurrences than did cirrhotics. Overall survival was similar for both groups. Prospective studies of noncirrhotic HCC patients in Asia and Western countries may inform surveillance and treatment.