
In the Phase 3 REALIZE study, 662 genotype 1 hepatitis C virus (HCV)-infected patients with prior peginterferon/ribavirin treatment failure (including relapers, partial, and null responders) were randomized to 12 weeks of telaprevir given immediately (T12/PR48) or following 4 weeks of peginterferon/ribavirin (lead-in T12/PR48), or 12 weeks of placebo (PR48), combined with a total of 48 weeks of peginterferon alfa-2a/ribavirin. Sustained virologic response (SVR) rates were 64% (T12/PR48), 66% (lead-in T12/PR48), and 17% (PR48). This analysis aimed to characterize treatment outcomes and viral variants emerging in telaprevir-treated patients not achieving SVR. HCV NS3•4A population sequencing was performed at baseline, during treatment, and follow-up. Telaprevir-resistant variants were classified into lower-level (3- to 25-fold 50% inhibitory concentration [IC(50)] increase: V36A/M, T54A/S, R155I/K/M/T, and A156S) and higher-level (>25-fold IC(50) increase: V36M+R155K and A156T/V) resistance. Resistant variants were uncommon at baseline. Overall, 18% (52%, 19%, and 1% of prior null and partial responders and relapers, respectively) of telaprevir-treated patients had on-treatment virologic failure, with no significant difference with or without a lead-in. Virologic failure during the telaprevir-treatment phase was predominantly associated with higher-level resistance; virologic failure during the peginterferon/ribavirin-treatment phase was associated with higher- or lower-level, or wildtype variants, depending on genotype. Relapse occurred in 9% of patients completing assigned treatment and was generally associated with lower-level resistant variants or wildtype. Resistant variants were no longer detectable by study end (median follow-up of 11 months) in 58% of non-SVR patients. CONCLUSION: In REALIZE, variants emerging in non-SVR, telaprevir-treated patients were similar irrespective of the use of a lead-in and were consistent with those previously reported. In most patients, resistant variants became undetectable over time.

BACKGROUND: The purpose of this study was to assess the efficacy and safety of low-dose peg-IFN α-2a plus ribavirin on the treatment of patients with chronic hepatitis C virus (HCV) infection. PATIENTS AND METHODS: A total of 243 HCV patients treated with different doses of peg-IFN α-2a plus ribavirin were stratified into three groups. End-of-treatment response (ETR) and sustained viral response (SVR) were evaluated for efficacy. Adverse events and laboratory abnormalities were conducted for safety. RESULTS: ETR and SVR in group I were obtained in 83.9% and 68.9% of the patients, separately, which was similar to groups II (84.1% and 68.3%) and III (81.7% and 66.7%). The received peg-IFN α-2a dose was not the independent factor-related SVR in our population (OR, 1.31; 95% CI, 0.94-1.81; P = 0.106). The frequency of no adverse events reported in group III (24.7%) was significantly higher than that in group I (11.5%) and group II (12.7%) (P = 0.036). CONCLUSIONS: The peg-IFN α-2a 90 μg/week plus ribavirin is as effective as, and better tolerated than, peg-IFN α-2a standard dose with ribavirin in the treatment of chronic hepatitis C. This low-dose combination achieves high SVR rates and may be cost-saving.


BACKGROUND/AIMS: Peginterferon (PEG-IFN) + ribavirin (RBV) combination therapy is the current standard of care for chronic hepatitis C. However, more than half of the patients cannot achieve sustained viral response (SVR). In Japan, the clinical benefit of retreatment with PEG-IFN + RBV combination retreatment is still unknown. METHODS: We collected clinical data in 106 chronic hepatitis C patients who failed to achieve SVR with PEG-IFNα-2b + RBV combination therapy and were retreated with PEG-IFNα-2a + RBV. This retrospective study examined the efficacy of retreatment with PEG-IFNα-2a + RBV by evaluating the time to eradication of hepatitis C virus RNA, early virological response (EVR), and SVR. We compared the results of the previous therapy and retreatment in terms of efficacy and analyzed the factors influencing SVR. RESULTS: The SVR rates in the non-responders and relapers were 11 and 53%, respectively. EVR and prolonged treatment duration were associated with SVR. We also found that a prior response to PEG-IFN + RBV therapy was more important than the Interleukin-28B genotype for predicting the response to retreatment. CONCLUSIONS: Retreatment with PEG-IFNα-2a + RBV should be considered for relapers and partial responders. Our results suggest that prolonged administration is also favorable for EVR cases to attain a higher SVR.


OBJECTIVE: Decreased appetite is one of the main factors that influences quality of life of patients with chronic liver diseases. The reason for appetite disorders remains unclear but taste perturbations are one of the postulated causes. The potential role of taste alterations and,
connected to these, appetite disorders in chronic hepatitis C (CHC) patients are poorly investigated. The aim of this study was to evaluate potential taste alterations (dysgeusia) including all five tastes (sweet, salty, bitter, sour and umami) in CHC patients. METHODS: Forty CHC patients (16 men and 24 women) infected with genotype 1 hepatitis C virus participated in this study. All the patients had a compensated liver disease and were being treated with any agents. One hundred and ten healthy volunteers were matched to the patients by age and sex. The study included gustatory tests (taste recognition threshold, taste intensity with hedonic perception) and analysis of the pleasure derived from eating. RESULTS: In CHC patients, the recognition threshold of umami taste was increased (P<0.01) and the intensity of sweet taste perception was higher (P<0.05). The hedonic response did not differ between the groups. A significant increase in declared pleasure derived from eating (P<0.001 to P<0.05) was also observed. Some differences in case of the patients with more advanced disease were also found. CONCLUSION: Alterations in taste, especially umami and sweet taste disorders, may alter real food perception and lead to a reduction in food intake in some CHC patients.


BACKGROUND AND GOALS: There are limited data on the extent to which medical providers adhere to practice guidelines for the antiviral treatment of patients with chronic hepatitis C virus (HCV) infection. As representative of overall provider adherence to practice guidelines, provider adherence to specific recommendations regarding rapid virologic response (RVR) was assessed. STUDY: From the Department of Veterans Affairs' Clinical Case Registry, all patients with HCV genotype 1 who initiated peginterferon and ribavirin between January 1, 2007 and December 31, 2008 were identified. The rate of testing for RVR was determined. Patient, provider, and facility characteristics were assessed to determine the factors that predicted improved provider adherence. For patients who achieved RVR, the overall treatment duration was calculated as a secondary measure of provider adherence. RESULTS: About one half of the cohort (54%) had HCV RNA testing for RVR. Among several significant predictors, testing for RVR was more likely in gastroenterology/hepatology specialty clinics, by midlevel providers such as nurse practitioners and physician assistants, and in facilities with a higher volume of HCV patients. Most patients who achieved RVR completed a treatment course within the recommended range. However, 27% of the cohort received more or less than the recommended duration of treatment, thereby unnecessarily increasing their risk for adverse events or decreasing their potential for cure. CONCLUSIONS: More aggressive education is needed to improve provider adherence to HCV antiviral treatment guidelines and optimize the outcomes of HCV patients, especially with the recent approval of complicated direct-acting antiviral regimens.


We conducted this double-blind, parallel-group, placebo-controlled, randomized, multiple ascending dose study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics
of GS-9851 (formerly PSI-7851) in treatment-naïve patients infected with hepatitis C virus (HCV) genotype 1. Thirty-two patients received active doses up to 400 mg of GS-9851 once-daily for 3 days. GS-9851 and the metabolite GS-566500 (formerly PSI-352707) were rapidly cleared from the plasma, with t(½) values of approximately 1 hour for GS-9851 and 3 hours for GS-566500. Accumulation (21%) was observed only for GS-331007 (formerly PSI-6206) after multiple dosing. GS-331007 was the primary drug-related moiety in the plasma and urine. Increases in GS-9851, GS-566500, and GS-331007 C(max) and AUC were less than dose-proportional particularly at the highest doses. The decline in plasma HCV RNA levels was dose-dependent and a mean maximal change from baseline of -1.95 log(10) IU/mL was obtained for 400 mg GS-9851 compared with -0.090 log(10) IU/mL for placebo. Most patients had a decrease in HCV RNA ≥1.0 log(10) IU/mL after 3 days' dosing with 400 mg GS-9851. No virologic resistance was observed. GS-9851 was generally well-tolerated with no notable differences in adverse event frequency across doses. The pharmacokinetic profile observed in this study was similar to that seen in a single ascending dose study in healthy subjects.


BACKGROUND: Viral kinetics and host interleukin 28B (IL-28B) genotype determine treatment outcome in hepatitis C virus genotype 1 (HCV-1) infection. OBJECTIVES: We aimed to explore the interplay between interferon responsiveness at treatment week 4 and IL28B genotype in the achievement of a sustained virological response (SVR; undetectable HCV RNA 24-weeks after end-of-treatment). STUDY DESIGNS: Rs8099917 genotypes were determined in 528 HCV-1 patients with peginterferon/ribavirin. Interferon responsiveness were evaluated by the degree of week 4 viral reduction: <1 log(10) IU/mL, 1-2 logs(10) IU/mL, 2-3 logs(10) IU/mL, 3-4 logs(10) IU/mL and ≥4 logs(10) IU/mL reduction and/or undetectable HCV RNA, respectively. RESULTS: The SVR rate was significantly higher in patients with great interferon responsiveness at week 4. A great interferon responsiveness was associated with younger age (P<0.0001), lower body mass index (P=0.0056), lower aspartate aminotransferase levels (P=0.0009), higher hemogloblin concentration (P=0.0033), higher platelet counts (P<0.0001), male gender (P<0.0001) and rs809997 TT-genotype (P<0.0001). Comparing to non-TT genotype patients, TT genotype patients had a significantly higher SVR rate with moderate viral reduction (1-3 logs(10) IU/mL) at week 4 (58.9% vs. 18.2%, P<0.001), and the SVR rate did not differ between TT/non-TT patients on the extreme ends (<1 or >3 log(10) IU/mL reduction) of week 4 interferon responsiveness. For non-TT genotype carriers who were with <3 logs(10) reduction, none (0/15) could have a complete early virological response and only 10.9% (7/64) of the patients had an SVR. CONCLUSIONS: More profound interferon responsiveness is mandatory for HCV-1 patients with unfavorable IL-28B genotype.
BACKGROUND: Preclinical data suggested all-trans retinoic acid (tretinoin) as a potential antiviral agent against chronic hepatitis C infection. AIMS: To assess efficacy, safety, and tolerability of tretinoin in combination with peg-interferon and ribavirin in genotype-1 infected patients with prior non-response. METHOD: We performed an open-label multicentre clinical trial. Patients were randomised to either receive additional tretinoin (45mg/m(2)/day) for 12 weeks (arm A), or peg-interferon and ribavirin alone (arm B). Primary endpoint was the slope of the third phase of viral decline (Mδ) as determined in an established kinetic model known to correlate with treatment outcome. Secondary endpoints were additional kinetic parameters, viral response rates, safety, and tolerability. RESULTS: 27 patients in arm A and 30 patients in arm B were treated per protocol until week 12. Viral kinetic parameters did not differ. Rates of early virological response (>2log(10) drop at week 12) were similar (10/27 versus 11/30 patients). In arm A, patients experienced a higher rate and intensity of adverse events, most commonly skin and mucosal dryness, and headache. CONCLUSION: Addition of tretinoin was safe and acceptably well tolerated. However, it did not influence viral kinetics and thus cannot be further considered as a treatment option.

Chronic hepatitis C virus (HCV) infection outcomes include liver failure, hepatocellular carcinoma (HCC), and liver-related death. OBJECTIVE: To assess the association between sustained virological response (SVR) and all-cause mortality in patients with chronic HCV infection and advanced hepatic fibrosis. DESIGN, SETTING, AND PATIENTS: An international, multicenter, long-term follow-up study from 5 large tertiary care hospitals in Europe and Canada of 530 patients with chronic HCV infection who started an interferon-based treatment regimen between 1990 and 2003, following histological proof of advanced hepatic fibrosis or cirrhosis (Ishak score 4-6). Complete follow-up ranged between January 2010 and October 2011. MAIN OUTCOME MEASURES: All-cause mortality. Secondary outcomes were liver failure, HCC, and liver-related mortality or liver transplantation. RESULTS: The 530 study patients were followed up for a median (interquartile range [IQR]) of 8.4 (6.4-11.4) years. The baseline median (IQR) age was 48 (42-56) years and 369 patients (70%) were men. The Ishak fibrosis score was 4 in 143 patients (27%), 5 in 101 patients (19%), and 6 in 286 patients (54%). There were 192 patients (36%) who achieved SVR; 13 patients with SVR and 100 without SVR died (10-year cumulative all-cause mortality rate, 8.9% [95% CI, 3.3%-14.5%] with SVR and 26.0% [95% CI, 20.2%-28.4%] without SVR; P < .001). In time-dependent multivariate Cox regression analysis, SVR was associated with reduced risk of all-cause mortality (hazard ratio [HR], 0.26; 95% CI, 0.14-0.49; P < .001) and reduced risk of liver-related mortality or transplantation (HR, 0.06; 95% CI, 0.02-0.19; P < .001), the latter occurring in 3 patients with SVR and 103 without SVR. The 10-year cumulative incidence rate of liver-related mortality or transplantation was 1.9% (95% CI, 0.0%-4.1%) with SVR and 27.4% (95% CI,
22.0%-32.8%) without SVR (P < .001). There were 7 patients with SVR and 76 without SVR who developed HCC (10-year cumulative incidence rate, 5.1%; 95% CI, 1.3%-8.9%; vs 21.8%; 95% CI, 16.6%-27.0%; P < .001), and 4 patients with SVR and 111 without SVR who experienced liver failure (10-year cumulative incidence rate, 2.1%; 95% CI, 0.0%-4.5%; vs 29.9%; 95% CI, 24.3%-35.5%; P < .001). CONCLUSION: Among patients with chronic HCV infection and advanced hepatic fibrosis, sustained virological response to interferon-based treatment was associated with lower all-cause mortality.


AIM: The historical standard of care for patients with chronic hepatitis C virus (HCV) was peginterferon (PEG IFN) and ribavirin combination therapy, yielding sustained virological response (SVR) rates of 38-52% in HCV genotype 1 patients. This study evaluated a novel three-drug regimen of nitazoxanide and high-dose ribavirin as lead-in therapy, followed by PEG IFN-α-2a in triple therapy. METHODS: A prospective, open-label pilot study was conducted in treatment-naive patients with HCV genotype 1. Patients received nitazoxanide 500 mg twice a day for 2 weeks, then nitazoxanide plus ribavirin 1400 mg/day for 2 weeks, then nitazoxanide plus ribavirin plus PEG IFN-α-2a 180 μg weekly for 12 weeks, followed by ribavirin plus PEG IFN-α-2a for 12 weeks (48 weeks if HCV RNA negative after week 24). Primary outcome was SVR. Other outcomes included very rapid virological response (VRVR), rapid virological response (RVR), early virological response (EVR), end-of-treatment response (ETR), and safety and tolerability. RESULTS: Thirty-three patients with a mean age of 46 years, detectable HCV RNA (64% with <600 000 IU/mL), and METAVIR fibrosis scores (F1:F2:F3) of 15%:49%:36% were enrolled. Outcomes were as follows: SVR, 67% (22/33); VRVR, 39% (13/33); RVR, 48% (16/33); EVR, 70% (23/33); and ETR, 67% (22/33). Most patients required at least one growth factor. Two patients discontinued because of adverse events. CONCLUSION: This three-drug regimen was effective in achieving SVR in patients with HCV genotype 1. No patients relapsed, and the toxicity profile was favorable. Further studies on the role of nitazoxanide in the treatment of chronic HCV are warranted.


Increased GGT activity is associated with liver injury and with mortality in the general population. Less is known about its association with HCV outcomes. We examined the GGT as a predictor of both virological response to treatment and long-term clinical outcomes in the Hepatitis C Anti-viral Treatment Against Cirrhosis Trial (HALT-C). METHODS: HALT-C enrolled patients with advanced liver disease (Ishak fibrosis score >=3) in 2 phases: a lead-in to establish lack of sustained viral response with full dose pegylated interferon (IFN) and ribavirin followed by a 3.5 year randomized trial with low-dose IFN. Low-dose IFN did not prevent liver disease progression, and patients were then followed for up to an additional 5 years off therapy. Analyses were performed for 1319 patients who had GGT measured prior to initiation of treatment. Increases in risk with each increase in quintile of GGT (10-57, 58-89, 90-139, 140-
230, 231-2000IU/L) were determined by logistic regression for treatment response or Cox regression for clinical outcomes. **RESULTS:** Baseline GGT was associated with male sex, non-white ethnicity, diabetes and insulin resistance, IL28B rs12979860 CT and TT genotypes, and numerous markers of liver disease injury and severity. In the lead-in phase, increasing GGT was strongly associated with diminished week 20 response, end of treatment response and sustained virological response in both univariate and multivariate analyses controlling for factors known to be associated with treatment response (p<0.0001). GGT was also associated with all clinical outcomes in univariate and multivariate analysis (p<0.05) except for hepatocellular carcinoma (p=0.46 in multivariate analysis). **CONCLUSION:** GGT is an independent predictor of both virological response and clinical outcomes among patients with advanced liver disease due to HCV.


The study of Hepatitis C Virus (HCV) has benefitted from the use of the Huh7 cell culture system, but until recently there were no other widely used alternatives to this cell line. Here we render another human hepatoma cell line, Hep3B, permissive to the complete virus life cycle by supplementation with the liver-specific microRNA miR-122, known to aid HCV RNA accumulation. When supplemented, Hep3B cells produce J6/JFH-1 virus titres indistinguishable from those produced by Huh7.5 cells. Interestingly, we were able to detect and characterize miR-122-independent replication of di-cistronic replicons in Hep3B cells. Further, we show that Argonaute-2 (Ago2) is required for miR-122-dependent replication, but dispensable for miR-122-independent replication, confirming Ago2's role in mediating the activity of miR-122. Thus Hep3B cells are a model system for the study of HCV, and miR-122 independent replication is a model to identify proteins involved in the function of miR-122.


**OBJECTIVES:** No study evaluated circulating chemokine (CXC motif) ligand (CXCL)9 in 'patients with mixed cryoglobulinaemia and hepatitis C virus chronic infection' (MC+HCV). We aimed to measure CXCL9, IFN-γ and TNF-α in a series of MC+HCV to correlate these parameters to different clinical phenotypes. **METHODS:** Serum CXCL9, IFN-γ and TNF-α were assayed in 54 MC+HCV, in 54 patients with HCV chronic infection (HCV+) and in 54 sex- and age-matched controls. **RESULTS:** MC+HCV showed significantly higher mean CXCL9 than HCV+ patients (p=0.01; ANOVA) or controls (p=0.0001; ANOVA), in particular in 21 cryoglobulinaemic patients with active vasculitis compared to those without (p<0.001; ANOVA). Serum IFN-γ (in patients with detectable IFN-γ) and TNF-α were significantly higher in MC+HCV than in controls (p<0.05, Mann-Whitney U test; p<0.0001, Mann-Whitney U-test; respectively). CXCL9, evaluated by classes of IFN-γ (IFN-γ<2; 2<IFN-γ<5; IFN-γ>5 pg/mL), or TNF-α (TNF-α<2; 2<TNF-α<10; TNF-α>10 pg/mL), showed a progressive, but not significant,
increase of circulating values. When the combination of high circulating levels of IFN-γ and TNF-α (IFN-γ>2 and TNF-α>10 pg/mL vs. IFN-γ<2 and/or TNF-α<10 pg/mL) was evaluated, significantly higher CXCL9 levels were observed (p<0.01; ANOVA). **CONCLUSIONS:** We demonstrated markedly high serum levels of CXCL9 in MC+HCV (vs. HCV+ patients or healthy controls), significantly associated with the presence of active vasculitis. A strong relation among high levels of circulating IFN-γ, TNF-α and serum CXCL9 has been shown in MC+HCV. Larger patients' series will be needed to evaluate the relevance of serum CXCL9 determination as clinico-prognostic marker of MC+HCV.


Oxidized low density lipoprotein (oxLDL) has been reported as an inhibitor of hepatitis C virus (HCV) cell entry making it the only known component of human lipid metabolism with an antiviral effect on HCV. However, several questions remain open including its effect on full length cell culture grown HCV (HCVcc) of different genotypes or on other steps of the viral replication cycle, its mechanism of action and whether endogenous oxLDL shares the anti-HCV properties of in vitro generated oxLDL. We combined molecular virology tools with oxLDL serum measurements in different patient cohorts to address these questions. We found that oxLDL inhibits HCVcc at least as potently as HCV pseudoparticles. There was moderate variation between genotypes with genotype 4 appearing most oxLDL sensitive. Intracellular RNA replication and assembly and release of new particles were unaffected. HCV particles entering target cells lost oxLDL sensitivity with time kinetics parallel to anti-SR-BI but significantly earlier than anti-CD81 suggesting that oxLDL acts by perturbing the interaction between HCV and SR-BI. Finally, in chronically HCV infected individuals endogenous serum oxLDL levels did not correlate with viral load, but in HCV-negative sera high endogenous oxLDL had a negative effect on HCV infectivity in vitro. **IN CONCLUSION** oxLDL is a potent pan-genotype HCV entry inhibitor that maintains its activity in the context of human serum and targets an early step of HCV entry.


Hepatitis C virus (HCV) is the most common chronic blood-borne infection in the United States with the majority of patients becoming chronically infected and a subset (20%) progressing to cirrhosis and hepatocellular carcinoma. Individual variations in immune responses may help define successful resistance to infection with HCV. We have examined the immune response in primary macrophages from patients who have spontaneously cleared HCV (viral load negative, VL-, n = 37) compared to HCV genotype 1 chronically infected (VL+) subjects (n=32) and found that macrophages from VL- subjects have an elevated baseline expression of Toll-like receptor 3 (TLR3). Macrophages from HCV patients were stimulated ex vivo through the TLR3 pathway and assessed using gene expression arrays and pathway analysis. We found elevated TLR3 response genes and pathway activity from VL- subjects. Furthermore, macrophages from VL- subjects showed higher production of IFN-β and related IFN response genes by Q-PCR, and
increased phosphorylation of STAT-1 by immunoblot. Analysis of polymorphisms in TLR3 revealed a significant association of intronic TLR3 polymorphism (rs13126816) with the clearance of HCV and the expression of TLR3. Of note, PBMCs from the same donors showed opposite changes in gene expression, suggesting ongoing inflammatory responses in PBMCs from VL+ HCV patients. Our results suggest that an elevated innate immune response enhances HCV clearance mechanisms and may offer a potential therapeutic approach to increase viral clearance.


Two single nucleotide polymorphisms rs12979860C/T and rs8099917T/G, around Interleukin-28B (IL28B) locus have been extensively investigated in their association with hepatitis C virus (HCV) spontaneous clearance. However, with the variable and even inconsistent results, it is necessary to conduct a meta-analysis. A literature search was conducted to seek articles about genetic variation of IL28B and spontaneous clearance of HCV. Odds ratio with 95% confidential interval were calculated to estimate their relationship. Furthermore, meta-regression analysis was performed to search for potential affective factors. A total of 8 studies including 2460 patients with chronic HCV infection and 1052 individuals with spontaneous HCV clearance met inclusion criteria, in which seven studies describing rs12979860 and three studies describing rs8099917. Analysis performed in Caucasian populations indicated that rs12979860CC and rs8099917TT contributed to HCV spontaneous clearance in both dominant model (CC vs. CT+TT, P<1×10(-4); TT vs. TG+GG, P<10(-4), respectively) and co-dominant model (CC vs. CT, P<1×10(-4), CC vs. TT, P<1×10(-4); TT vs. TG, P<10(-4), TT vs. GG, P=0.012, respectively). Meta-regression analysis suggested that male proportion (P=1×10(-5)) and mean age (P=1×10(-3)) might weaken the effect of rs12979860CC, but HCV genotype 1/4 (P=4×10(-4)) might contribute to it. IL28B rs12979860CC and rs8099917TT genotypes contribute to spontaneous HCV clearance in Caucasians.


Low oxygen tension exerts a significant effect on the replication of several DNA and RNA viruses in cultured cells. In vitro propagation of the hepatitis C virus (HCV) has thus far been studied under atmospheric oxygen levels despite the fact that the liver tissue microenvironment is hypoxic. In this study, we investigated the efficiency of HCV production in actively dividing or differentiated human hepatoma cells cultured under low or atmospheric O(2) tensions. By using both HCV replicons and infection-based assays, low oxygen condition was found to enhance HCV RNA replication whereas virus entry and RNA translation were not affected. Hypoxia signaling pathway-focused DNA microarray and real-time quantitative reverse transcription-PCR (qRT-PCR) analyses revealed an upregulation of genes related to hypoxic stress, glycolytic metabolism, cell growth and proliferation when cells were kept under low (3% v/v) O(2) tension, likely reflecting cell adaptation to anaerobic conditions. Interestingly, hypoxia-mediated enhancement of HCV replication correlated directly with the increase in anaerobic glycolysis and creatine kinase B (CKB) activity leading to elevated ATP production.
Surprisingly, activation of hypoxia-inducible factor-α (HIF-α) was not involved in the elevation of HCV replication. Instead, a number of oncogenes, known to be associated with glycolysis were upregulated and evidence was obtained that these oncogenes contribute to hypoxia-mediated enhancement of HCV replication. Finally, in liver biopsies of HCV-infected patients, the levels of hypoxia and anaerobic metabolism markers correlated with HCV RNA levels. These results provide new insights into the impact of O(2) tension on the intricate HCV-host cell interaction.

**HIV/HCV COINFECTION**


**BACKGROUND:** Boceprevir represents a new treatment option for hepatitis C (HCV)-infected patients, including those with HCV/human immunodeficiency virus coinfection; however, little is known about pharmacokinetic interactions between boceprevir and antiretroviral drugs.

**METHODS:** A randomized, open-label study to assess the pharmacokinetic interactions between boceprevir and ritonavir-boosted protease inhibitors (PI/r) was conducted in 39 healthy adults. Subjects received boceprevir (800 mg, 3 times daily) for 6 days and then received PI/r as follows: atazanavir (ATV) 300 mg once daily, lopinavir (LPV) 400 mg twice daily, or darunavir (DRV) 600 mg twice daily, each with ritonavir (RTV) 100 mg on days 10-31, plus concomitant boceprevir on days 25-31. **RESULTS:** Boceprevir decreased the exposure of all PI/r, with area under the concentration-time curve [AUC] from time 0 to the time of the last measurable sample geometric mean ratios of 0.65 (90% confidence interval [CI], .55-.78) for ATV/r; 0.66 (90% CI, .60-.72) for LPV/r, and 0.56 (90% CI, .51-.61) for DRV/r. Coadministration with boceprevir decreased RTV AUC during a dosing interval τ (AUC(τ)) by 22%-36%. ATV/r did not significantly affect boceprevir exposure, but boceprevir AUC(τ) was reduced by 45% and 32% when coadministered with LPV/r and DRV/r, respectively. Overall, treatments were well tolerated with no unexpected adverse events. **CONCLUSIONS:** Concomitant administration of boceprevir with PI/r resulted in reduced exposures of PI and boceprevir. These drug-drug interactions may reduce the effectiveness of PI/r and/or boceprevir when coadministered.


Interferon (IFN) preactivation, interleukin-28B (IL28B) alleles, and liver fibrosis act as predictors of response to antiviral therapy against hepatitis C. We aimed to verify if blood IFN concentration, a putative biomarker of interferon preactivation, might depend on carriage of a given IL28B genotype and/or advanced hepatic fibrosis. The study population included 187 hepatitis C patients (75 of whom were HIV coinfected), who were genotyped for the rs12979860 polymorphism and staged non-invasively by transient elastography. Blood IFN, measured by an enzyme immunoassay, was detectable in 68/187 patients (36%). Seventy-three patients (39%) were C/C homozygotes, 25 (13%) were T/T homozygotes, and 89 (48%) were heterozygotes. The fibrosis stage was F0-F1 in 70 patients (37%), F2-F3 in 54 patients (29%), and F4 in 63.
patients (34%). IFN levels were higher among patients with HIV coinfection (p=0.044) and patients with better renal function (p=0.041), without association with the IL28B genotype or the hepatitis C stage. From the multivariate analysis, the only independent predictor of higher level of IFN was the age of patients (p=0.019), whereas independent predictors of a fibrosis stage ≥F2 were age (p=0.007), belonging to the HIV/HCV group (p=0.048) and current alcohol consumption (p=0.008). In conclusion, a sizable proportion of HCV carriers have detectable IFN levels that do not indicate a greater severity of disease or display any relationships to specific rs12979860 variants.


BACKGROUND: We and others have shown that primary hepatitis C (HCV) infection of HIV-infected men causes early onset liver fibrosis. Little is known about the long-term natural history of the liver disease in these HIV-infected men, however. METHODS: We followed a cohort of HIV-infected men with primary HCV infection in New York City. Four men who were not cured after their primary HCV infection rapidly developed decompensated cirrhosis and were followed longitudinally. RESULTS: Three of the four men had AIDS at the time of primary HCV infection. Decompensated cirrhosis subsequently occurred in all four within 17 months to six years after primary HCV infection. Three died within eight years of primary HCV infection and one survived after liver transplantation done two years after primary HCV infection. The most rapid progression occurred in the two men with the lowest CD4 counts at the time of HCV infection. Liver histopathology was most consistent with HCV-induced damage even though some had exposures to other potential hepatotoxins. CONCLUSIONS: Primary HCV infection resulted in decompensated cirrhosis and death within two to eight years in four HIV-infected men. The rapid-onset of fibrosis due to primary HCV infection in HIV-infected men cannot therefore be considered benign. The rate of continued progression to liver failure may be proportional to the degree of underlying immunocompromise caused by HIV infection. More research is needed to better define the mechanisms behind accelerated liver damage.


BACKGROUND: Liver diseases are the leading causes of death in human immunodeficiency virus (HIV)-positive persons since the widespread use of combination antiretroviral treatment (cART). Most of these deaths are due to hepatitis C (HCV) or B (HBV) virus coinfections. Little is known about other causes. Prolonged exposure to some antiretroviral drugs might increase hepatic mortality. METHODS: All patients in the Data Collection on Adverse Events of Anti-HIV Drugs study without HCV or HBV coinfection were prospectively followed from date of entry until death or last follow-up. In patients with liver-related death, clinical charts were reviewed using a structured questionnaire. RESULTS: We followed 22 910 participants without hepatitis virus coinfection for 114 478 person-years. There were 12 liver-related deaths (incidence, 0.10/1000 person-years); 7 due to severe alcohol use and 5 due to established ART-
related toxicity. The rate of ART-related deaths in treatment-experienced persons was 0.04/1000 person-years (95% confidence interval, .01, .10). **CONCLUSIONS:** We found a low incidence of liver-related deaths in HIV-infected persons without HCV or HBV coinfection. Liver-related mortality because of ART-related toxicity was rare.

**Absence of liver steatosis in HIV-HCV co-infected patients receiving regimens containing tenofovir or abacavir.** Borghi V, Bisi L, Manzini L, Cossarizza A, Mussini C. Infection. 2012 Dec 9. [Epub ahead of print]


**BACKGROUND:** In human immunodeficiency virus-hepatitis C virus (HIV-HCV) co-infected patients, steatosis has been independently associated with a number of antiretroviral drugs, including stavudine, especially in patients with non-3 HCV genotypes. We retrospectively investigated the presence of steatosis among HIV-HCV co-infected and HCV mono-infected patients, and the role of tenofovir disoproxil fumarate (TDF) or abacavir (ABC) in determining hepatic steatosis. **METHODS:** Liver steatosis was retrospectively evaluated in all consecutive biopsies performed in the period 2000-2008 in HCV mono-infected and HIV-HCV co-infected patients. A steatosis rate of >5% was considered to be significant, and a multivariate logistic analysis was performed to evaluate factors associated with steatosis. **RESULTS:** In total, 393 HCV-infected patients underwent liver biopsy during the study period, of whom 205 (52.2%) were co-infected with HIV. A steatosis rate of >5% was diagnosed in 33.0% of HCV mono-infected and in 47.8% of HIV-HCV co-infected patients (P = 0.003). The rate of steatosis was higher in patients resuming antiretroviral therapy (54.7%) than in naïve patients (33.3%; P = 0.006). When the overall population was considered, steatosis was associated to HCV genotype 3 [odds ratio (OR) 4.53, 95% confidence interval (CI) 2.71-7.58; P < 0.001]. In terms of the use of nucleos(t)ide drugs in HIV co-infected patients, multivariate analysis showed that only in patients with HCV genotypes other than genotype 3 was steatosis related to the use of stavudine (OR 5.38, 95% CI 1.18-24.53; P = 0.03). The use of TDF (OR 1.07, 95% CI 0.39-2.88; P = 0.898) or ABC (OR 0.592, 95% CI 0.09-4.07; P = 0.594) was not associated with steatosis. **CONCLUSION:** In HCV mono-infected and HIV-HCV co-infected patients, steatosis appears to be a virus-mediated effect of HCV genotype 3. In HIV patients infected with HCV genotypes other than genotype 3, the risk of developing steatosis was higher in those patients resuming antiretroviral regimens containing old drugs rather than the new antiretrovirals.


Coinfection with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) is common. HIV infection and treatment are associated with hypercoaguability; thrombosis in HCV is under-investigated. Proposed markers of hemostasis in HIV include higher D-dimer, Factor VIII% and Plasminogen Activator Inhibitor-1 (PAI-1Ag), and lower total Protein S% (TPS), but have not been examined in HCV. We assessed the independent association of HCV with these four measures of hemostasis in a multicenter, prospective study of HIV: the Women's Intergency HIV Study (WIHS). We randomly selected 450 HCV-infected (anti-HCV+ with detectable plasma HCV RNA) and 450 HCV-uninfected (anti-HCV-) women. HCV was the main exposure of interest in regression models. 443 HCV+ and 425 HCV- women were included. HCV+
women had higher Factor VIII% (124.4% ± 3.9 vs. 101.8% ± 3.7, p < 0.001) and lower TPS (75.7% ±1.1 vs. 84.3% ±1.1, <0.001) than HCV-, independent of HIV infection and viral load; there was little difference in PAI-1Ag or log10 D-dimer. After adjustment for confounders, these inferences remained. HIV infection was independently associated with higher Factor VIII% and log10 D-dimer, and lower TPS. HCV was independently associated with higher Factor VIII% and lower TPS consistent with hypercoaguability. Higher Factor VIII % and D-dimer and lower total Protein S % were also strongly associated with HIV infection and levels of HIV viremia, independent of HCV infection. Further investigation is needed to determine if there is increased thrombotic risk from HCV. Studies examining hemostasis markers in HIV infection must also assess the contribution of HCV infection.


OBJECTIVES: Accurate prediction of sustained virological response (SVR) to pegylated interferon-α (Peg-IFN) plus ribavirin in HIV/hepatitis C virus (HCV)-coinfected patients could improve the management of these patients. We aimed to develop a model to predict SVR to Peg-IFN/ribavirin in HIV/HCV-coinfected individuals combining HCV genotype and baseline HCV RNA load with interleukin 28B and low-density lipoprotein receptor genetic variations.

METHODS: Three hundred and twelve treatment-naive HIV/HCV-coinfected patients receiving Peg-IFN/ribavirin were analysed in an on-treatment approach. One hundred and eighty-one of them were included in the development group and 131 in the validation population. The predictive model was obtained from a logistic regression equation including the above-mentioned variables. The areas under the receiver operating characteristic (AUROC) curves (95% CI), sensitivity and specificity, as well as negative and positive predictive values, were calculated. RESULTS: SVR was achieved by 88 (48.6%) patients from the development group and 68 (51.9%) individuals from the validation group. The AUROC curve values (95% asymptotic CI) were 0.83 (0.77-0.89) for the development group and 0.84 (0.77-0.91) for the validation group. Using two cut-off values, maximum specificity and sensitivity were 89.7% and 96.6%, respectively, with a negative predictive value for SVR of 88.9% and a positive predictive value of 83.6%. Thirteen (7.2%) individuals were misclassified using these cut-off values.

CONCLUSIONS: This model represents a reliable and easily applicable tool to individually evaluate the probability of achieving an SVR to Peg-IFN/ribavirin among HIV/HCV-coinfected patients.

COMPLEMENTARY AND ALTERNATIVE MEDICINE


Recent data suggest that vitamin A modulate the expression of type I interferon receptor enhancing the anti-replication effect of interferon-α on hepatitis C virus (HCV). This study aimed to investigate the prevalence of vitamin A deficiency among patients with chronic HCV infection and to assess whether vitamin A deficiency could be associated with unresponsiveness...
to interferon based antiviral therapy. The analysis included 199 consecutive treatment-naive chronic hepatitis C patients in whom pre-treatment serum vitamin A and 25-OH vitamin D were measured; 119 healthy blood donors were used as controls. Median (inter-quartile range) serum vitamin A in HCV positive patients was significantly lower than in controls: 256 ng/mL (128-440) Vs 742 (624-942, p<0.0001). Overall sustained viral response was achieved in 122/199 patients, 46/109 infected by difficult to treat HCV genotypes. In these latter, 39/104 (37.5%) were non responders. At multivariate analysis, non-response to antiviral therapy was predicted by carriage of IL-28B T/* genotypes, baseline serum levels of γGT > 60 IU/mL, of HCV RNA > 600,000 IU/mL, of vitamin A ≤ 100 ng/mL and the cumulative dose of ribavirin ≤ 80%.

Seventeen patients (9.0%) had both serum levels of vitamin A ≤ 100 ng/mL and of vitamin D ≤ 20 ng/mL; the presence of the combined vitamin A and D deficiency was found to be a strong independent predictor of non-response to antiviral therapy. CONCLUSIONS: a high percentage of patients with chronic HCV infection present serum vitamin A deficiency. This condition is associated with non-response to antiviral therapy.


BACKGROUND: Coffee is associated with a reduced risk of hepatocellular carcinoma in patients with chronic C hepatitis. This prospective trial was aimed at assessing the mechanisms underlying coffee-related protective effects. METHODS: Forty patients with chronic hepatitis C were randomized into two groups: the first consumed 4 cups of coffee/day for 30 days, while the second remained coffee "abstinent". At day 30, the groups were switched over for a second month. RESULTS: At baseline, aspartate aminotransferase and alanine aminotransferase were lower in patients drinking 3-5 (Group B) than 0-2 cups/day (Group A) (56±6 vs 74±11/60±3 vs 73±7U/L p=0.05/p=0.04, respectively). HCV-RNA levels were significantly higher in Group B [(6.2±1.5)×10(5) vs (3.9±1.0)×10(5) IU/mL, p=0.05]. During coffee intake, 8-hydroxydeoxyguanosine and collagen levels were significantly lower than during abstinence (15±3 vs 44±16 8-hydroxydeoxyguanosine/10(5)deoxyguanosine, p=0.05 and 56±9 vs 86±21ng/mL, p=0.04). Telomere length was significantly higher in patients during coffee intake (0.68±0.06 vs 0.48±0.04 Arbitrary Units, p=0.006). Telomere length and 8-hydroxydeoxyguanosine were inversely correlated. CONCLUSION: In chronic hepatitis C coffee consumption induces a reduction in oxidative damage, correlated with increased telomere length and apoptosis, with lower collagen synthesis, factors that probably mediate the protection exerted by coffee with respect to disease progression.


Upon screening of plant-derived natural products against hepatitis C virus (HCV) in the replicon system, we demonstrated that lucidone, a phyto compound, isolated from the fruits of Lindera erythrocarpa Makino, significantly suppressed HCV RNA levels with an EC(50) value of 15 ± 0.5 μM and 20 ± 1.1 μM in HCV replicon and JFH-1 infectious assays, respectively. There was no significant cytotoxicity observed at high concentrations, with a CC(50) value of 620 ± 5 μM.
In addition, lucidone significantly induced heme oxygenase-1 (HO-1) production and led to the increase of its product biliverdin for inducing anti-viral interferon response and inhibiting HCV NS3/4A protease activity. Conversely, the anti-HCV activity of lucidone was abrogated by blocking HO-1 activity or silencing gene expression of HO-1 or NF-E2-related factor 2 (Nrf2) in the presence of lucidone, indicating that the anti-HCV action of lucidone was due to the stimulation of Nrf-2-mediated HO-1 expression. Moreover, the combination of lucidone and interferon-α, the protease inhibitor telaprevir, the NS5A inhibitor BMS-790052, or the NS5B polymerase inhibitor PSI-7977, synergistically suppressed HCV RNA replication. These findings suggest that lucidone could be a potential lead or supplement for development of new anti-HCV agent in the future.

**Epidemiology, Diagnostics, and Miscellaneous Works**


**INTRODUCTION:** Epidemiologic links between herpes simplex virus type-2 (HSV-2) and hepatitis C virus (HCV) exist but are poorly characterized. Seroprevalence studies of HSV-2 in veteran populations with chronic HCV infection are lacking. **METHODS:** The authors reviewed the medical histories and results of the HerpeSelect IgG (Focus Diagnostics, Cypress, CA) of 244 HCV-infected male veterans engaged in care. All patients were human immunodeficiency virus negative and >99% defined themselves as heterosexual. **RESULTS:** Using the manufacturer's recommended cutoff for positive results (>1.1), 51.5% of HCV-infected veterans were seropositive for HSV-2. When increasing the cutoff to >3.5, 38.7% of persons were seropositive for HSV-2. Reports of previous diagnosis with genital ulcer disease (9/213; 4.3%) or genital herpes (4/213; 1.9%) were rare. **CONCLUSIONS:** HSV-2 infection commonly occurred in the study sample of HCV-infected veterans but was infrequently recognized. Future studies should optimize the use of type-specific serologic screening tests in HCV-infected persons. The high prevalence of HSV-2 in this population merits further investigation into any potential biologic interactions between these common viral infections.


The results from clinical trials testing new direct-acting antivirals (DAAs) for chronic hepatitis C were the major focus of interest at the 2012 annual meeting of the European Association for the Study of the Liver. Besides triple combinations, in which any one of the new DAAs is given along with peginterferon-α/ribavirin, clinical trials exploring interferon-free oral regimens combining several DAAs attracted major attention. The good tolerance, broad hepatitis C virus (HCV) genotype activity, and high resistance barrier of sofosbuvir make this nucleotide analogue one of the most promising DAAs. Among HCV protease inhibitors, the safety, potency, and convenient dosing of simeprevir, asunaprevir, faldaprevir, and ABT-450/r were particularly highlighted. Among NS5A inhibitors, the good performance of daclatasvir encourages further clinical development. Finally, intriguing results were released about the role of interleukin 28B
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(IL-28B) polymorphisms using interferon-free regimens, indirectly supporting the role of innate immunity for clearing HCV definitively.


**BACKGROUND:** In settings such as needle-stick injuries or intravenous drug abuse, immediate knowledge of the anti-hepatitis C virus (HCV) serostatus instead of waiting for the results of a laboratory-based test can be important to guide further medical procedures and appropriate hygienic advises. Thus, a rapid on-site anti-HCV test was evaluated in daily clinical routine and compared with a laboratory-based certified assay. **PATIENTS AND METHODS:** Ten microliters of serum or EDTA whole blood was analyzed using a chromatographic immunoassay (Toyo anti-HCV test). Results were available on-site 5-15 min after sample centrifugation. The Architect anti-HCV test served as a reference method. **RESULTS:** Sera of 189 patients were analyzed (without HCV infection: n=105; HCV infection: n=84). The assay was evaluable in 185 cases (98%). The sensitivity and specificity were 99 and 88%, respectively. With EDTA whole blood, the test was evaluable in 47/52 samples (90%). Forty-six of 47 evaluable EDTA tests were concordant with serum results. The one HCV patient with an unevaluable serum test was diagnosed correctly with the EDTA sample. **CONCLUSION:** The rapid chromatographic anti-HCV immunoassay has limited specificity, which impairs clinical practicability. A positive result warrants re-evaluation with a certified serologic assay.


The worldwide prevalence of HCV infection is between 1% and 8% in pregnant women and between 0.05% and 5% in children. Yet the pathogenesis of hepatitis C during pregnancy and in the neonatal period remains poorly understood. Mother-to-child transmission (MTCT), a leading cause of pediatric HCV infection, takes place at a rate of <10%. Factors that increase the risk of MTCT include high maternal HCV viral load and coinfection with HIV-1 but, intriguingly, not breastfeeding and mode of delivery. Pharmacological prevention of MTCT is not possible at the present time because both pegylated interferon alfa and ribavirin are contraindicated for use in pregnancy and during the neonatal period. However, this may change with the recent introduction of direct acting antiviral agents. This review summarizes what is currently known about HCV infection during pregnancy and childhood. Particular emphasis is placed on how pregnancy-associated immune modulation may influence the progression of HCV disease and impact MTCT, and on the differential evolution of perinatally acquired HCV infection in children. Taken together, these developments provide insights into the pathogenesis of hepatitis C and may inform strategies to prevent the transmission of HCV from mother to child.

BACKGROUND: Chronic hepatitis C virus (HCV) may progress to advanced liver disease (ALD), including decompensated cirrhosis and/or hepatocellular carcinoma (HCC). ALD can lead to significant clinical and economic consequences, including liver transplantation. This study evaluated the health care costs associated with ALD among HCV infected patients in a Medicaid population. METHODS: Using Florida Medicaid claims data, cases were patients with at least 1 diagnosis of HCV or prescription therapy for HCV (ribavirin plus interferon, peginterferon, or interferon alfacon-1) prior to an incident ALD-related diagnosis ("index event") between 1999 and 2007. ALD-related conditions included decompensated cirrhosis, HCC, or liver transplant. A cohort of HCV patients without ALD (comparison group subjects) were matched 1-to-1 based on age, sex, and race. Baseline and follow-up were the 12 months prior to and following index, respectively; with both periods allowing for a maximum one month gap in eligibility. For both case and comparison patient cohorts, per-patient-per-eligible month (PPPM) costs were calculated as total Medicaid paid amount for each patient over their observed number of eligible months in follow-up, divided by the patient's total number of eligible months. A generalized linear model (GLM) was constructed controlling for age, race, Charlson score, alcoholic cirrhosis, and hepatitis B to explore all-cause PPPM costs between study groups. The final study group included 1,193 cases and matched comparison patients (mean age: 49 years; 45% female; 54% white, 23% black, 23% other). RESULTS: The majority of ALD-related diagnoses were for decompensated cirrhosis (92%), followed by HCC (6%) and liver transplant (2%). Cases had greater comorbidity (mean Charlson score: 3.1 vs. 2.3, P < 0.001). All-cause inpatient use up to 1-year following incident ALD diagnosis was significantly greater among cases with ALD (74% vs. 27%, P < 0.001). In the GLM, cases had 2.39 times greater total adjusted mean all-cause PPPM costs compared to the comparison group ($4,956 vs. $1,735 respectively; P < 0.001). Among cases, mean total unadjusted ALD-related costs were $1,356 PPPM, which were largely driven by inpatient costs ($1,272). CONCLUSIONS: Our results suggest that among patients diagnosed with HCV, the incremental costs of developing ALD are substantial, with inpatient stays as the main driver of these increased costs.


To evaluate the capacity of Versant HCV genotype assay (LiPA) 2.0 to identify hepatitis C virus (HCV) genotypes, 110 serum samples were collected from chronic hepatitis C patients. Three methods were compared: core sequence analysis, NS5B sequence analysis and the INNO-LiPA assay. The result showed that 102 (92.7%) of the samples were amplified in either or both regions, of which 97 were amplified in the core region and 62 were amplified in the NS5B region. Correlation analysis showed that amplification rates of subgenomic regions were associated with viral loads. Basic local alignment search tool (BLAST) and phylogenetic analysis showed that the 102 samples were classified into 5 categories: subtype 1b, 2a, 3a, 3b and 6a at frequencies of 61.8% (63), 9.8% (10), 3.9% (4), 3.9% (4) and 20.6% (21), respectively. Compared with sequencing methods, 66.7% (68) of the 102 samples were identified completely.
by LiPA 2.0, whereas 19.6% (20) were assigned incompletely (indistinguishable or not identified subtype) and 13.7% (14) were misclassified. Of 21 genotype 6a samples, 11 were mistyped as 1b. **In conclusion**, LiPA 2.0 was not suitable for identifying HCV genotypes in the samples tested, whereas core sequence analysis remained an ideal method for genotyping HCV.


HCV RNA viral load (VL) monitoring is a well-established diagnostic tool for managing chronic hepatitis C patients. HCV RNA VL results are used to make treatment decisions with the goal of therapy to achieve an undetectable VL result. Therefore, a sensitive assay with high specificity in detecting and accurately quantifying HCV RNA across genotypes is critical. Additionally, a lower sample volume requirement is desirable for the laboratory and patient. This study evaluates the performance characteristics of a second generation real-time PCR assay, the COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, version 2.0 (CAP/CTM HCV Test, v2.0), designed with a novel dual-probe approach and an optimized automated extraction and amplification procedure. The new assay demonstrated a limit of detection and lower limit of quantification of 15 IU/mL across all HCV genotypes; and was linear from 15 to 100,000,000 IU/mL with high accuracy (<0.2 log(10) difference) and precision (SD=0.04-0.22 log(10)). Specificity of 100% in 600 HCV sero-negative specimens was demonstrated without cross reactivity or interference. Correlation to the COBAS® AmpliPrep/COBAS® TaqMan® HCV Test (version 1) was good (n=412 genotype 1-6 samples, R(2)=0.88; R(2)=0.94 without n=105 genotype 4 samples). Paired plasma and serum samples showed similar performance (n=25, R(2)=0.99). Sample input volume was reduced from 1mL to 0.65mL in the second version. The CAP/CTM HCV Test, v2.0 demonstrated excellent performance and sensitivity across all HCV genotypes using a lower sample volume. The new HCV RNA VL assay has performance characteristics that make it suitable for use with currently available DAAs.


**BACKGROUND:** Detection of hepatitis C virus (HCV) reinfection and intercalation (ie, intermittent recurrent bouts of viremia with homologous virus interspersed with aviremic periods) requires extensive and frequent evaluation and viral sequencing. **METHODS:** HCV infection outcomes were studied prospectively in active injection drug users with recurrent HCV RNA-positive tests after serial negative results. HCV viremia and viral sequences (Core/E1) were assessed from monthly blood samples. **RESULTS:** Viral clearance, reinfection, and intercalating infection were all detected. Among 44 participants with apparently resolved HCV (26 incident HCV clearers and 18 enrolled with already resolved infection), 36 (82%) remained persistently HCV RNA negative, but 8 demonstrated intermittent recurrent viremia. Four of these (50%) had confirmed reinfection with a heterologous virus; 3 demonstrated viral intercalation, and 1 was not classifiable as either. Estimated incidence of first reinfection was 5.4 per 100 person-years (95% confidence interval, 2.0-14.5). Six (75%) participants, including 3 of 4 with reinfection, demonstrated sustained viral clearance for a median of 26 months since last HCV
RNA test. **CONCLUSIONS:** These results show that frequent monitoring and viral sequencing are required to correctly assess HCV outcomes and estimate incidence of reinfection (which was previously overestimated). Sustained clearance may take many months and occur after episodes of reinfection and viral intercalation. Three of 4 subjects who had confirmed reinfection showed evidence of long-term clearance. Viral intercalation occurs with significant frequency. Further studies of these events, especially immunological, are needed to inform HCV clinical care and vaccine development.


The Pacific Northwest of the US is a large, sparsely populated region. A telehealth programme called Project ECHO (Extension for Community Health Outcomes) was tested in this region in 2009. Weekly videoconferences were held in the areas of hepatitis C, chronic pain, integrated addictions and psychiatry, and HIV/AIDS. Rural clinicians presented cases to a panel of experts at an academic medical centre and received management advice and access to best practices. During the trial, more than 900 clinicians participated, and more than 700 patient cases were presented. At the end of June 2012, a total of 23 videoconference clinics for hepatitis C had been held, 16 clinics in addiction and psychiatry, 97 in chronic pain and 13 in HIV/AIDS. The Project ECHO model improves access to health care. It may provide a way to bring specialist care to rural areas in developing countries.

**Liver Cancer**


Previous studies have investigated extrahepatic multiple primary malignancy (EHPM) associated with hepatocellular carcinoma (HCC). However, its correlation with viral infection, such as hepatitis B virus (HBV) or hepatitis C virus (HCV), has not been examined. The aim of this study is to investigate the association between EHPM and hepatitis infection in HCC patients. A total of 412 patients who underwent surgical resection for primary HCC were enrolled. Viral infection was evaluated by serum HBV surface antigen (HBs Ag) and HCV antibody (HCV Ab). Sixty-eight (16.5%) patients had one or more EHPM. The most frequent EHPM was gastric cancer (n = 32) in this cohort. No statistical significance was observed in the distribution of viral infection and incidence of entire EHPM. However, HCV Ab, HBs Ag, and negative status for both were correlated with the frequency of gastric (P = 0.0194), urinary tract (P = 0.0067), and breast cancer (P = 0.0036), respectively. Infection of Helicobacter pylori was investigated by immunohistochemistry in gastric EHPM and resulted that 20 out of 21 analyzed cases were negative for Helicobacter pylori. Although it should be verified by well-designed large cohort studies, the current results suggested correlation between HCV infection and gastric cancer, HBV infection and urinary tract cancer and viral hepatitis-free status and breast cancer in HCC patients.

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BACKGROUND: Because hepatocellular carcinoma (HCC) has important angiogenic activity, the expression of angiopoietin-2 (Ang-2) may have a pathogenic role. The information about the influence of serum Ang-2 (sAng-2) in patients with HCC is scarce. AIMS: The aim was to assess the association between sAng-2 levels and characteristics of tumor and liver disease in patients with HCC. Methods. sAng-2 concentrations in peripheral (sAng-2-P) and hepatic (sAng-2-H) veins were analyzed by ELISA in 33 patients with chronic liver disease who underwent a splanchnic hemodynamic study. Thirty-two patients received treatment for HCC. RESULTS: The median age was 61 years and 79% were male. Hepatitis C infection (70%) was the main etiology. Most patients were Child-Pugh grade A (72.7%). sAng-2-P and sAng-2-H were well correlated (r = 0.95; p < 0.0001). A significant association was found between sAng-2-H and lobar tumor extension, vascular thrombosis, BCLC staging, infiltrating pattern, abnormal alpha-fetoprotein level, fulfillment of the Milan criteria, and performance of nonsystemic treatment. sAng-2-H also showed a significant correlation with the MELD score (r = 0.49; p = 0.007), albumin (r = -0.63; p < 0.001), and HVPG (r = 0.44; p = 0.02). Eleven patients received treatment with radiofrequency ablation and eight with transarterial chemoembolization. HCC treatment did not influence the sAng-2 concentration while the necrosis response to treatment was not influenced by previous sAng-2 levels. CONCLUSIONS: Ang-2 seems to play an important role in the angiogenic processes of HCC and its serum levels are associated with tumor characteristics and invasive behavior. Our results suggest that Ang-2 is not related with treatment response and its level is not modified by treatment.


In the United States, the peak hepatitis C virus (HCV) antibody prevalence of 4% occurred in persons born in the calendar years 1940-1965. The goal of this study was to examine observed and projected age-specific trends in the demand for liver transplantation (LT) among patients with HCV-associated liver disease stratified by concurrent hepatocellular carcinoma (HCC). All new adult LT candidates registered with the Organ Procurement and Transplantation Network for LT between 1995 and 2010 were identified. Patients who had primary, secondary, or text field diagnoses of HCV with or without HCC were identified. There were 126,862 new primary registrants for LT, and 52,540 (41%) had HCV. The number of new registrants with HCV dramatically differed by the age at calendar year, and this suggested a birth cohort effect. When the candidates were stratified by birth year in 5-year intervals, the birth cohorts with the highest frequency of HCV were as follows (in decreasing order): 1951-1955, 1956-1960, 1946-1950, and 1941-1945. These 4 birth cohorts, spanning from 1941 to 1960, accounted for 81% of all new registrants with HCV. A 4-fold increase in new registrants with HCV and HCC occurred between the calendar years 2000 and 2010 in the 1941-1960 birth cohorts. By 2015, we anticipate that an increasing proportion of new registrants with HCV will have HCC and be ≥60 years old (born in or before 1955). In conclusion, the greatest demand for LT due to HCV-associated liver disease is occurring among individuals born between 1941 and 1960. This
demand appears to be driven by the development of HCC in patients with HCV. During the coming decade, the projected increase in the demand for LT from an aging HCV-infected population will challenge the transplant community to reconsider current treatment paradigms.


**OBJECTIVE:** Increasing evidence suggests the efficacy of maintenance therapy with interferon (IFN) for chronic hepatitis C (CHC) in reducing the risk of hepatocellular carcinoma (HCC). The aim of this study was to determine clinical characteristics on the risk of occurrence of HCC in CHC patients receiving maintenance IFN therapy. **METHODS:** A total of 55 patients were treated in a single center with PEG-IFNα-2a monotherapy for CHC and evaluated for variables predictive of the occurrence of HCC. **RESULTS:** The cumulative incidences of HCC were 0.092, 0.117 and 0.161 at 3, 5 and 7 years, respectively. Serum ALT level (>40 IU/l) in the 6th month after commencement of IFN therapy and BMI >25 were associated with shorter time-to-HCC emergence using multivariate analysis (relative risk 16.034, p = 0.01 for ALT >40 IU/l; relative risk 6.020, p = 0.026 for BMI >25, respectively). The IL28B SNP was extracted as a significant factor for the occurrence of HCC. **CONCLUSIONS:** Maintenance therapy with the use of long-term low-dose PEG-IFNα-2a is effective for preventing HCC occurrence irrespective of the IL28B SNP, at least for a subset of CHC patients. The initial response of serum ALT levels and BMI provides a prognostic value for determining the risk of developing HCC later in life.


**OBJECTIVES:** A unique causative aspect of hepatocellular carcinoma (HCC) is a gender difference in its incidence. To determine the specific factors that contribute to a male predominance, we analyzed the clinicopathological factors, and genetic and epigenetic alterations of HCCs in male and female patients. **METHODS:** We retrospectively analyzed three cohorts of patients: the first cohort consisted of 547 patients identified with the first event of HCC, the second cohort included 176 HCC patients, and the third 127 patients with chronic hepatitis C (CHC). **RESULTS:** Male patients were found to have HCC more frequently than female patients in cases of non-cirrhotic liver (p = 0.0030 by the χ(2) test), especially in hepatitis C-positive cases. However, there were no gender-specific differences in the genetic and epigenetic alterations of cancer-related genes. Deposition of iron was more severe in male CHC patients than in female patients. **CONCLUSIONS:** Male patients with CHC develop HCC more frequently when they have a non-cirrhotic liver than do female patients. This gender difference could be, at least partially, attributed to a different degree of iron deposition, which contributes to the development of HCC in the absence of liver cirrhosis in men with CHC.

The impact of amino acid (aa) 70 substitution in the core region on hepatocarcinogenesis and survival for liver-related death in patients of hepatitis C virus (HCV) genotype 1b (HCV-1b), who had not received antiviral therapy, is unknown. The relationships among aa 70 substitution, IL28B genotype, and hepatocarcinogenesis are also not clear. A total of 1,181 consecutive HCV-infected patients, who had not received antiviral therapy, were included in a follow-up study to determine predictive factors of hepatocarcinogenesis and survival for liver-related death. The cumulative hepatocarcinogenesis rates in HCV-1b of Gln70(His70) (glutamine (histidine) at aa 70) were significantly higher than those in HCV-1b of Arg70 (arginine at aa 70) and HCV-2a/2b. The cumulative survival rates for liver-related death in HCV-1b of Gln70(His70) were significantly lower than those in HCV-1b of Arg70 and HCV-2a/2b. Multivariate analysis identified gender (male), age (≥60 years), albumin (<3.9 g/dL), platelet count (<15.0 × 10^4 /mm^3), aspartate aminotransferase (≥67 IU/L), and HCV subgroup (HCV-1b of Gln70(His70)) as determinants of both hepatocarcinogenesis and survival rates for liver-related death. In HCV-1b patients, the cumulative change rates from Arg70 to Gln70(His70) by direct sequencing were significantly higher than those from Gln70(His70) to Arg70. In patients of Arg70 at the initial visit, the cumulative change rates from Arg70 to Gln70(His70) in IL28B rs8099917 non-TT genotype were significantly higher than those in the TT genotype. **Conclusion:** Substitution of aa 70 in the core region of HCV-1b is an important predictor of hepatocarcinogenesis and survival for liver-related death in HCV patients who had not received antiviral therapy. The IL28B genotype might partly affect changes over time of dominant amino acid in core aa 70 of HCV-1b.