
BACKGROUND: HCV-TARGET is a longitudinal observational study of chronic hepatitis C virus (HCV) patients treated with direct-acting anti-viral agents (DAAs) in a US consortium of 90 academic and community medical centres. AIM: To assess utilisation of response-guided therapy (RGT) and sustained virological response (SVR) of a large cohort of patients.

METHODS: Patients received peginterferon (PEG-IFN), ribavirin and either telaprevir or boceprevir. Demographical, clinical and virological data were collected during treatment and follow-up. RGT and treatment futility stopping rules was assessed at key time points.

RESULTS: Of 2084 patients, 38% had cirrhosis and 56% had received prior treatment for HCV. SVR rates were 31% (95% CI: 24-40) and 50% (95% CI: 44-56) in boceprevir patients with and without cirrhosis, respectively. SVR rates were 46% (95% CI: 42-50) and 60% (95% CI: 57-64) in telaprevir patients with and without cirrhosis, respectively. Early clearance of virus, IL28B genotype, platelet counts and diabetes were identified as predictors of SVR among boceprevir patients, while early clearance of virus, IL28B, cirrhosis, HCV subtype, age, haemoglobin, bilirubin and albumin levels were identified as predictors of SVR for telaprevir patients.

CONCLUSIONS: In academic and community centres, triple therapy including boceprevir or telaprevir led to SVR rates somewhat lower than those noted in large phase 3 clinical trials. Response rates were consistently higher among patients without cirrhosis compared to those with cirrhosis regardless of DAA used and prior treatment response.


Treatment options for patients with hepatitis C virus (HCV) genotype 3 infection are limited, with the currently approved all-oral regimens requiring 24-week treatment and the addition of ribavirin. This phase 3 study (ALLY-3; http://www.ClinicalTrials.gov NCT02032901) evaluated the 12-week regimen of daclatasvir (pangenotypic NS5A inhibitor) plus sofosbuvir (pangenotypic NS5B inhibitor) in patients infected with genotype 3. Patients were either treatment-naive (n=101) or treatment-experienced (n=51) and received daclatasvir 60mg plus...
sofosbuvir 400mg once daily for 12 weeks. Co-primary endpoints were the proportions of treatment-naive and treatment-experienced patients achieving a sustained virologic response at posttreatment Week 12 (SVR12). SVR12 rates were 90% (91/101) and 86% (44/51) in treatment-naive and treatment-experienced patients, respectively; no virologic breakthrough was observed, and ≥99% of patients had a virologic response at the end of treatment. SVR12 rates were higher in patients without cirrhosis (96% [105/109]) than in those with cirrhosis (63% [20/32]). Five of 7 patients who previously failed treatment with a sofosbuvir-containing regimen and 2 of 2 patients who previously failed treatment with an alisporivir-containing regimen achieved SVR12. Baseline characteristics, including gender, age, HCV RNA levels, and IL28B genotype, did not impact virologic outcome. Daclatasvir plus sofosbuvir was well tolerated; there were no adverse events leading to discontinuation and only 1 serious adverse event on-treatment, which was unrelated to study medications. The few treatment-emergent grade 3/4 laboratory abnormalities that were observed were transient. Conclusion: A 12-week regimen of daclatasvir plus sofosbuvir achieved SVR12 in 96% of patients with genotype 3 infection without cirrhosis and was well tolerated. Additional evaluation to optimize efficacy in genotype 3-infected patients with cirrhosis is underway.


**BACKGROUND AND OBJECTIVE:** To assess within the ANRS CO20-CUPIC cohort whether the viral load (VL) at week2/week6 for telaprevir/boceprevir-based triple therapy, respectively, was predictive of sustained virological response (SVR) in patients with hepatitis C virus (HCV) infection and to study the relevance of this measurement to early diagnose drug resistance. **METHODS:** Observational study of HCV genotype 1 patients with compensated cirrhosis (Child-Pugh A), non-responders to a prior course of interferon (IFN)-based therapy and who started triple therapy. Patients received either 12 weeks of telaprevir in combination with PEG-IFN/ribavirin (RBV), then 36 weeks of PEG-IFN/RBV, or 4 weeks of PEG-IFN/RBV, then 44 weeks of PEG-IFN/RBV and boceprevir. **RESULTS:** A total of 262 patients were analyzed. For telaprevir-treated patients, 28% had undetectable VL at W2 of whom 81% achieved SVR12 whereas 67% had undetectable VL at W4 of whom 67% achieved SVR12. For boceprevir-treated patients 20% had undetectable VL at W6 and 86% of them achieved SVR12 whereas 36% had undetectable VL at W8 among whom 73% achieved SVR12. Five telaprevir-treated patients had a VL increase between W2 and W4 after a decrease between D0 and W2. Four of them did not achieve SVR12. Similarly, six boceprevir-treated patients had a VL increase between W6 and W8 after a decrease between D0 and W6. Five did not reach SVR12. **CONCLUSIONS:** The assessment of HCV RNA level after two weeks of triple therapy in cirrhotic non-responder patients is a good predictor of SVR. This assessment was useful to do an early diagnosis of viral breakthrough.

**BACKGROUND:** Natural killer (NK) cells are an important element of innate immunity against viruses, although their numbers decrease in the liver during chronic HCV infection. NK cells express a large panel of inhibitory and activating receptors. The most polymorphic of these are killer cell immunoglobulin-like receptors (KIRs) which are encoded by multiple genes that may be present or absent in given individuals depending on their genotype. This variability results in differential susceptibility to viral infections and diseases, including HCV infection and its consequences. **AIMS AND METHODS:** The aim of this study was to test whether chronic infection with HCV and the viremia levels are associated with any KIR gene in the Polish population. We typed 301 chronically HCV-infected patients and 425 non-infected healthy individuals for the presence or absence of KIR genes and their ligands, HLA-C C1 and C2 groups as well as HLA-B and HLA-A Bw4-positive alleles. **RESULTS:** We found that males, but not females, possessing KIR2DS2 and KIR2DL2 genes had a 1.7 higher probability to become chronically HCV-infected than males negative for these genes (p = 0.0213). In accord with this, centromeric B region, containing KIR2DS2 and KIR2DL2 genes, was also associated with chronic HCV infection in males. In addition, patients of both genders possessing KIR2DS3 but not KIR2DS5 gene exhibited, on average, 2.6 lower level of viremia than HCV-infected individuals with other genotypes (p = 0.00282). This was evident in those infected at a young age. KIR2DS3-positive patients also had lower mean levels of bilirubin than KIR2DS3-negative ones (p = 0.02862). **CONCLUSION:** Our results suggest a contribution of the KIR2DS2 and KIR2DL2 genes (cenB haplotype) to the susceptibility to chronic HCV infection, and an association of the KIR2DS3 gene in the absence of KIR2DS5 with low viremia levels.


**BACKGROUND & AIMS:** The efficacy and tolerability of faldaprevir, a potent hepatitis C virus (HCV) NS3/4A protease inhibitor, plus peginterferon and ribavirin was assessed in a double-blind, placebo-controlled phase 3 study of treatment-naïve patients with HCV genotype-1 infection. **METHODS:** Patients were randomly assigned (1:2:2) to peginterferon/ribavirin plus: placebo (arm 1, n=132) for 24 weeks; faldaprevir (120 mg, once daily) for 12 or 24 weeks (arm 2, n=259); or faldaprevir (240 mg, once daily) for 12 weeks (arm 3, n=261). In arms 2 and 3, patients with early treatment success (HCV RNA <25 IU/mL at week 4 and undetectable at week 8) stopped all treatment at week 24. Other patients received peginterferon/ribavirin until week 48 unless they met futility criteria. The primary endpoint was sustained virologic response 12 weeks post-treatment (SVR12). **RESULTS:** SVR12 was achieved by 52%, 79%, and 80% of patients in arms 1, 2, and 3, respectively (estimated difference for arms 2 and 3 versus arm 1: 27%, 95% confidence interval 17%-36%; and 29%, 95% confidence interval, 19%-38%, respectively; P<.0001 for both). Early treatment success was achieved by 87% (arm 2) and 89% (arm 3) of patients, of whom 86% and 89% achieved SVR12. Adverse event rates were similar among groups; few adverse events led to discontinuation of all regimen components. **CONCLUSIONS:**
Faldaprevir plus peginterferon/ribavirin significantly increased SVR12, compared with peginterferon/ribavirin, in treatment-naïve patients with HCV genotype-1 infection. There do not seem to be any differences in responses of patients given once-daily 120 or 240 mg faldaprevir.


BACKGROUND: It is unclear whether the course of cirrhosis and its prognosis are related to the amount of collagen in the liver. AIM: To determine whether fibrosis, assessed by collagen proportionate area (CPA) in patients with compensated cirrhosis, is associated with the presence of oesophageal varices, and predict disease decompensation during the follow-up period.

METHODS: We prospectively evaluated 118 consecutive patients with compensated cirrhosis to correlate fibrosis, assessed by CPA in liver biopsies, with the presence of oesophageal varices (OV) and with the rate of liver decompensation (LD) development during a median follow-up of 72 months. RESULTS: At baseline 38 (32.2%) patients had OV and during the follow-up (median 72 months, IQR 47-91), 17 patients (14.4%) developed LD. The mean CPA value was different in patients with and without OV (14.8 ± 5.9% vs. 21.6 ± 9.5%, P < 0.001). The best CPA cut-off for OV by area under the receiver operating characteristic (AUROC) was ≥14% and with multivariate logistic analysis CPA was the only variable associated with OV (OR: 28.32, 95% CI: 6.30-127.28; P < 0.001). By AUROC analysis the best CPA cut-off to predict LD was 18.0%. By Cox regression multivariate analysis CPA ≥18% (HR: 3.99, 95% CI: 1.04-11.45; P = 0.036), albumin (HR: 0.12, 95% CI: 0.04-0.43; P = 0.001) and presence of OV (HR: 8.15, 95% CI: 2.31-28.78; P = 0.001) were independently associated with LD. CONCLUSION: Quantification of fibrosis by collagen proportionate area allows identification of patients with compensated HCV cirrhosis with a higher likelihood of clinically relevant portal hypertension and a higher risk of decompensation.


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tolerated; there were no adverse events leading to discontinuation and only 1 serious adverse event on-treatment, which was unrelated to study medications. The few treatment-emergent grade 3/4 laboratory abnormalities that were observed were transient. Conclusion: A 12-week regimen of daclatasvir plus sofosbuvir achieved SVR12 in 96% of patients with genotype 3 infection without cirrhosis and was well tolerated. Additional evaluation to optimize efficacy in genotype 3-infected patients with cirrhosis is underway.


BACKGROUND AND OBJECTIVE: To assess within the ANRS CO20-CUPIC cohort whether the viral load (VL) at week2/week6 for telaprevir/boceprevir-based triple therapy, respectively, was predictive of sustained virological response (SVR) in patients with hepatitis C virus (HCV) infection and to study the relevance of this measurement to early diagnose drug resistance. METHODS: Observational study of HCV genotype 1 patients with compensated cirrhosis (Child-Pugh A), non-responders to a prior course of interferon (IFN)-based therapy and who started triple therapy. Patients received either 12weeks of telaprevir in combination with PEG-IFN/ribavirin (RBV), then 36weeks of PEG-IFN/RBV, or 4weeks of PEG-IFN/RBV, then 44weeks of PEG-IFN/RBV and boceprevir. RESULTS: A total of 262 patients were analyzed. For telaprevir-treated patients, 28% had undetectable VL at W2 of whom 81% achieved SVR12 whereas 67% had undetectable VL at W4 of whom 67% achieved SVR12. For boceprevir-treated patients 20% had undetectable VL at W6 and 86% of them achieved SVR12 whereas 36% had undetectable VL at W8 among whom 73% achieved SVR12. Five telaprevir-treated patients had a VL increase between W2 and W4 after a decrease between D0 and W2. Four of them did not achieve SVR12. Similarly, six boceprevir-treated patients had a VL increase between W6 and W8 after a decrease between D0 and W6. Five did not reach SVR12. CONCLUSIONS: The assessment of HCV RNA level after two weeks of triple therapy in cirrhotic non-responder patients is a good predictor of SVR. This assessment was useful to do an early diagnosis of viral breakthrough.


OBJECTIVES: The Centers for Disease Control and Prevention (CDC) only recommends risk-based HCV screening for pregnant women in the United States. This study sought to determine the reliability of risk-based versus universal HCV screening for pregnant women in Egypt, a country with the world's highest HCV prevalence that also relies on risk-based screening, and to identify additional characteristics that could increase the reliability of risk-based screening. METHODS: Pregnant women attending the Cairo University antenatal clinic were tested for anti-HCV antibodies and RNA, and demographic characteristics and risk factors for infection were assessed. RESULTS: All 1250 pregnant women approached agreed to participate (100%) with a mean age of 27.4 ± 5.5 years (range:16-45). HCV antibodies and RNA were positive in 52 (4.2%) and 30 (2.4%) women respectively. After adjustment, only age (OR:1.08, 95%CI:1.002-1.16, p < 0.01), history of prior pregnancies (OR:1.20, 95%CI:1.01-1.43, p < 0.04), and working
in the healthcare sector (OR:8.68, 95%CI:1.72-43.62, p < 0.01), remained significantly associated with chronic HCV infection. **CONCLUSIONS:** Universal antenatal HCV screening was widely accepted (100%) and traditional risk-based screening alone would have missed 3 (10%) chronically infected women, thereby supporting universal screening of pregnant women whenever possible. Otherwise, risk-based screening should be modified to include history of prior pregnancy and healthcare employment.


**BACKGROUND:** Adequate ribavirin exposure is essential for optimal sustained virological response (SVR) rates in chronic hepatitis C virus (HCV) treatment. It has been proposed that the area under the curve (AUC0-4h) of the first weight-based ribavirin dose should be ≥1.755mg.h/L to guarantee the highest chance of SVR. Our ARRIBA concept comprises a test-dose of ribavirin to select the optimal starting-dose to achieve adequate exposure. This study aims to evaluate whether adequate exposure can be achieved after a dose advice based on the AUC0-4h of a single weight-based ribavirin test-dose. **METHODS:** (Formerly) HCV infected subjects received a single weight-based ribavirin test-dose (<75kg: 400mg; ≥75kg: 600mg) and the AUC0-4h was calculated. If ribavirin AUC0-4h was ≥1.755mg.h/L, subjects received the same dose 4 weeks later; if the AUC0-4h was <1.755mg.h/L, an adjusted dose was administered. The ribavirin AUC0-4h was recorded again. The primary outcome was the proportion of subjects with an AUC0-4h ≥1.755mg.h/L after the second dose. **RESULTS:** Twenty-six subjects were included. The geometric mean (95% CI) ribavirin AUC0-4h was 1.67 (1.44-1.92) mg.h/L with 9 subjects (35%) reaching the target AUC on day 1. Thus, on day 29, 17 subjects (65%) received an adjusted dose. The geometric mean (95% CI) AUC0-4h increased to 1.90 (1.62-2.21) mg.h/L and now 16 subjects (62%) had an AUC0-4h ≥1.755mg.h/L, which is significantly higher than day 1 (p<0.05). **CONCLUSIONS:** Our ARRIBA concept of a ribavirin test-dose, with dose adjustment if necessary, leads to an increased proportion of patients with an AUC ≥1.755mg.h/L compared to traditional weight-based ribavirin dosing.


**PURPOSE:** Chronic hepatitis C infection affects a large proportion of the world's population and can lead to significant morbidity and mortality. The standard of care for treatment of hepatitis C infection has been peginterferon and ribavirin, with or without a first-generation protease inhibitor. In late 2013 and early 2014, sofosbuvir and simeprevir obtained regulatory approval, offering the first possibility for all-oral treatment regimens. We provide a review of the clinical efficacy and safety of sofosbuvir- and simeprevir-containing regimens. **METHODS:** Studies were identified in PubMed using the terms sofosbuvir and simeprevir in combination with hepatitis C. Abstracts of additional studies presented at professional meetings but not yet published were also reviewed. All Phase 3 trials published by August 1, 2014, as well as Phase 2 studies for which there was not a corresponding Phase 3 trial, were included in the review. **FINDINGS:** Simeprevir was studied with peginterferon and ribavirin in 7 published Phase 3 trials, with overall efficacy rates of 59% to 100%. Sofosbuvir was studied with ribavirin and with or without peginterferon in 6 Phase 3 trials with overall efficacy rates of 50% to 93%. Patient groups with lower response rates tended to have cirrhosis and be older, men, and previous null
Simeprevir and sofosbuvir were studied in combination in 1 Phase 2a study with overall efficacy of 92%. Additional studies demonstrated the efficacy and safety of sofosbuvir regimens in patients before and after liver transplantation. Overall, the simeprevir- and sofosbuvir-containing regimens were tolerated better or as well as peginterferon and ribavirin regimens, with fatigue, headache, and nausea the most common adverse events. **IMPLICATIONS:** Results from numerous Phase 3 clinical trials indicate that sofosbuvir- and simeprevir-containing regimens are highly effective and safe for the treatment of chronic hepatitis C infection. The approval of these 2 agents has led to a complete overhaul of published guidelines, with sofosbuvir- and simeprevir-containing regimens included in preferred regimens.

**Efficacy and safety of simeprevir with PegIFN/ribavirin in naïve or experienced patients infected with chronic HCV genotype 4.** Moreno C1, Hezode C2, Marcellin P3, J Hepatol. 2015 Jan 14. pii: S0168-8278(15)00002-1. doi: 10.1016/j.jhep.2014.12.031. [Epub ahead of print] **BACKGROUND & AIMS:** Simeprevir (SMV) is a once-daily (QD), oral hepatitis C virus (HCV) NS3/4A protease inhibitor approved for treatment of genotype (GT)1 and GT4 infection. This Phase III, open-label, single-arm study (RESTORE; NCT01567735) evaluated efficacy/safety of SMV with peginterferon-α-2a/ribavirin (PR) in patients with chronic HCV GT4 infection. **METHODS:** 107 patients were included. Treatment-naïve (n=35) and prior relapse patients (n=22) received SMV 150mg QD+PR (12weeks), followed by PR alone (12 or 36 weeks, response-guided [HCV RNA <25IU/mL detectable/undetectable at Week 4 and <25 IU/mL undetectable at Week12]). Prior non-responders (partial, n=10; null, n=40) received SMV/PR (12weeks), followed by PR for 36 weeks. The primary endpoint was sustained virologic response 12 weeks after end of treatment (SVR12). **RESULTS:** Median age: 49.0 years; 28.0% Black/African; 7.5% IL28B CC; 28.8% METAVIR F4. Overall, 65.4% (70/107) of patients achieved SVR12 (82.9% [29/35] treatment-naïve; 86.4% [19/22] prior relapsers; 60.0% [6/10] prior partial responders; 40.0% [16/40] prior null responders). In treatment-naïve and prior relapser patients fulfilling response-guided criteria for 24 weeks of treatment (88.6% [31/35] and 90.9% [20/22]), SVR12 rates were high: 93.5% [29/31] and 95.0% [19/20], respectively. Overall on-treatment failure and relapse rates were 23.4% (25/107) and 14.6% (12/82), respectively. Adverse events (AEs) were mainly grade 1/2; serious AEs were infrequent (4.7%) and considered unrelated to SMV. **CONCLUSIONS:** Efficacy and safety of SMV 150mg QD for 12 weeks in treatment-naïve or -experienced patients with chronic HCV GT4 infection were in line with previous reports for HCV GT1 infection.

**Virological response after 6 week triple-drug regimens for hepatitis C: a proof-of-concept phase 2A cohort study.** Kohli A1, Osinusi A2, Sims Z3, et al. Lancet. 2015 Jan 12. pii: S0140-6736(14)61228-9. doi: 10.1016/S0140-6736(14)61228-9. [Epub ahead of print] **BACKGROUND:** Direct-acting antiviral drugs have a high cure rate and favourable tolerability for patients with hepatitis C virus (HCV). Shorter courses could improve affordability and adherence. Sofosbuvir and ledipasvir with ribavirin have high efficacy when taken for 8 weeks but not for 6 weeks. We assessed whether the addition of a third direct-acting antiviral drug to sofosbuvir and ledipasvir would allow a shorter treatment duration. **METHODS:** In this single-centre, open-label, phase 2A trial, we sequentially enrolled treatment-naïve patients with HCV genotype 1 infection into three treatment groups: 12 weeks of sofosbuvir and ledipasvir; 6 weeks of sofosbuvir, ledipasvir, and GS-9669; or 6 weeks of sofosbuvir, ledipasvir, and GS-9451. Patients and investigators were not masked to treatment assignment. The primary endpoint was
the proportion of patients with sustained viral response at 12 weeks after treatment completion (SVR12), assessed by serum HCV RNA concentrations lower than 43 IU/mL (the lower limit of quantification). We did an intention-to-treat analysis for the primary endpoint and adverse events. This study is registered with ClinicalTrials.gov, number NCT01805882.

Between Jan 11, 2013, and Dec 17, 2013, we enrolled 60 patients, and sequentially assigned them into three groups of 20. We noted an SVR12 in all 20 patients (100%, 95% CI 83-100) allocated to sofosbuvir and ledipasvir for 12 weeks; in 19 (95%, 75-100) of the 20 patients allocated to sofosbuvir, ledipasvir, and GS-9669 for 6 weeks (one patient relapsed 2 weeks after completion of treatment); and in 19 (95%, 75-100%) of the 20 patients allocated to sofosbuvir, ledipasvir, and GS-9451 for 6 weeks (one patient was lost to follow-up after reaching sustained viral response at 4 weeks). Most adverse events were mild and no patients discontinued treatment. Two serious adverse events occurred (pain after a post-treatment liver biopsy and vertigo), both unrelated to study drugs. **INTERPRETATION:** In this small proof-of-concept study, two different three-drug regimens that were given for 6 weeks resulted in high cure rates for HCV infection with excellent tolerability. Addition of a third potent direct-acting antiviral drug can reduce the duration of treatment required to achieve sustained viral response in patients with chronic HCV genotype 1 infection without cirrhosis.


**AIM:** Anemia is the most common adverse event in patients with chronic hepatitis C virus (HCV) treated with telaprevir (TVR) combined triple therapy. We examined the effects of drug dose adjustment on anemia and a sustained viral response (SVR) during combination therapy.

**MATERIAL AND METHODS:** This study enrolled 62 patients treated with TVR (2,250 mg) for 12 weeks plus pegylated interferon-alpha-2b and ribavirin for 24 weeks. The patients were assigned randomly to the TVR-standard or -reduced groups before treatment. At the occurrence of anemia (hemoglobin < 12 g/dL), the TVR-reduced group received 1500 mg TVR plus the standard dose of ribavirin, whereas the TVR-standard group received the standard TVR dose (2,250 mg) and a reduced dose of ribavirin (200 mg lower than prescribed originally). The safety and SVR at 24 weeks were compared between the TVR-standard (n = 28) and TVR-reduced (n = 25) groups. **RESULTS:** No differences in the proportion of patients who became HCV RNA-negative were detected between the TVR-standard and -reduced groups (72 and 72% at week 4, 79 and 84% at the end of treatment, and 76 and 80% at SVR24, respectively). Two groups had comparable numbers of adverse events, which led to the discontinuation of TVR in 14 patients of TVR-standard group and in 14 of TVR-reduced group. A lower incidence of renal impairment was observed in the TVR-reduced group (6%) than the TVR-standard group (11%, not statistically significant). **CONCLUSIONS:** TVR dose adjustment could prevent anemia progression without weakening the anti-viral effect during triple therapy in HCV-patients.


**BACKGROUND:** It is unclear whether the course of cirrhosis and its prognosis are related to the amount of collagen in the liver. **AIM:** To determine whether fibrosis, assessed by collagen
proportionate area (CPA) in patients with compensated cirrhosis, is associated with the presence of oesophageal varices, and predict disease decompensation during the follow-up period.

**METHODS:** We prospectively evaluated 118 consecutive patients with compensated cirrhosis to correlate fibrosis, assessed by CPA in liver biopsies, with the presence of oesophageal varices (OV) and with the rate of liver decompensation (LD) development during a median follow-up of 72 months. **RESULTS:** At baseline 38 (32.2%) patients had OV and during the follow-up (median 72 months, IQR 47-91), 17 patients (14.4%) developed LD. The mean CPA value was different in patients with and without OV (14.8 ± 5.9% vs. 21.6 ± 9.5%, P < 0.001). The best CPA cut-off for OV by area under the receiver operating characteristic (AUROC) was ≥14% and with multivariate logistic analysis CPA was the only variable associated with OV (OR: 28.32, 95% CI: 6.30-127.28; P < 0.001). By AUROC analysis the best CPA cut-off to predict LD was 18.0%. By Cox regression multivariate analysis CPA ≥18% (HR: 3.99, 95% CI: 1.04-11.45; P = 0.036), albumin (HR: 0.12, 95% CI: 0.04-0.43; P = 0.001) and presence of OV (HR: 8.15, 95% CI: 2.31-28.78; P = 0.001) were independently associated with LD. **CONCLUSION:** Quantification of fibrosis by collagen proportionate area allows identification of patients with compensated HCV cirrhosis with a higher likelihood of clinically relevant portal hypertension and a higher risk of decompensation.

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


Little is known on the immune status in liver and blood of chronic HCV patients long after therapy-induced viral clearance. In this study, we demonstrate that 4 years after clearance, regulation of HCV-specific immunity in blood by regulatory T-cells (Treg) and immunosuppressive cytokines IL-10 and TGF-β is still ongoing. Importantly, sampling of the liver 4 years after clearance shows that intrahepatic Treg are still present in all patients, suggesting that liver T-cells remain regulated. Identifying mechanisms that regulate HCV-specific memory T-cell responses after clearance is highly relevant for the development of protective vaccines, especially in patients at high-risk of reinfection.

**Determination of the HCV protease inhibitor telaprevir in plasma and dried blood spot by liquid chromatography tandem mass spectrometry.** Verweij-van Wissen CP1, de Graaff-Teulen MJ, de Kanter CT, Aarnoutse RE, Burger DM. Ther Drug Monit. 2015 Jan 26. [Epub ahead of print]

**BACKGROUND:** Telaprevir is a protease inhibitor used in the treatment of hepatitis C virus infection. Analytical methods for telaprevir should separate the compound from its R-diastereomer VRT-127394, which is 30-fold less active. The objective of this work was to develop liquid chromatography tandem mass spectrometer (LC-MS/MS) assays for telaprevir both in plasma as well as in dried blood spot (DBS), capable of stabilizing the equilibrium and chromatographically separating the two epimers. **METHODS:** Human plasma was acidified with formic acid and frozen within one hour after collection, to stabilize the equilibrium between the two telaprevir diastereomers ex vivo in plasma. After protein precipitation the sample was analyzed with LC-MS/MS. For the DBS assay, sampling paper was impregnated with citric acid solution to achieve stabilisation of the epimers on the sampling paper. DBS samples were
extracted before LC-MS/MS analysis. LC-MS/MS analysis comprised on line solid-phase extraction and separation on a C18 column with the mass spectrometer operating in TurboIonSpray negative ionization mode and performing multiple reaction monitoring.

**RESULTS:** The assays were linear over the concentration range of 0.1-10 mg/L in plasma and BS. Accuracies ranged from 97% to 106% in plasma and from 93% to 99% in DBS. Within- and between-day coefficients of variation were <7.9% in plasma and <9.3% in DBS. Human whole blood samples with hematocrit values of 27-47% gave reproducible quantitation results in the DBS assay and spot volume did not affect results of the DBS assay either. Acidified plasma with telaprevir was stable for 5 hours at 20C, and telaprevir on impregnated DBS paper was stable for at least 3 months at 4C or at 20C. **CONCLUSIONS:** An assay was developed and validated for the determination of telaprevir in human plasma, separating telaprevir from its R-diastereomer VRT-127394. In addition, a DBS assay was developed, which avoids immediate centrifuging, acidification and freezing of patient samples to stabilize the equilibrium between the two telaprevir diastereomers.


Dendritic cells (DCs) play an important role in the induction of the primary immune response to infection. DCs may express the tryptophan-catabolizing enzyme indolamine2,3-dioxygenase (IDO), which is an inducer of immune tolerance. Since there is evidence that chronic hepatitis C virus (HCV) infection leads to functional impairment of certain DC populations, we analyzed IDO expression in DCs and monocytes from chronically infected and recovered HCV patients. The IDO1 and -2 expression was significantly increased in the monocytes of chronic HCV patients, but interestingly, not in those from recovered patients. The myeloid DCs from chronically infected HCV patients also showed enhanced IDO1 expression, while no change in either IDO1 or -2 was found for plasmacytoid DCs. Up-regulation of IDO1 gene expression was confirmed by the presence of enhanced kynurenine/tryptophan ratios in the plasma from chronic HCV patients. Increased IDO1 and IDO2 expression was also observed in monocytes from healthy donors infected with an adapted mutant of JFH1-HCV ex vivo, confirming a direct effect of HCV infection. These changes in IDO expression could be prevented by treatment with the IDO inhibitor 1-methyl tryptophan (1-mT). Furthermore, maturation of monocyte-derived DCs from chronically infected HCV patients, as well as monocyte-derived DCs ex vivo infected with HCV, was impaired, but this was reversed by 1-mT treatment. This suggests that IDO inhibitors may be used to treat chronic HCV patients in vivo, in conjunction with current therapies, or to activate DCs from patients ex vivo, such that they can be administered back as a DC-based therapeutic vaccine.


Hepatitis C virus (HCV) infection is characterized by a high propensity for development of life-long viral persistence. An estimated 170 million people suffer from chronic hepatitis caused by HCV. Currently, there is no approved prophylactic HCV vaccine available. With the near disappearance of the most relevant animal model for HCV, the chimpanzee, we review the progression that has been made regarding prophylactic vaccine development against HCV. We
describe the results of the individual vaccine evaluation experiments in chimpanzees, in relation to what has been observed in humans. The results of the different studies indicate that partial protection against infection can be achieved, but a clear correlate of protection has thus far not yet been defined.

**Chronic hepatitis C virus infection triggers spontaneous differential expression of biosignatures associated with T cell exhaustion and apoptosis signaling in peripheral blood mononuclearocytes.** Barathan M1, Gopal K, Mohamed R, et al. Apoptosis. 2015 Jan 11. [Epub ahead of print]

Persistent hepatitis C virus (HCV) infection appears to trigger the onset of immune exhaustion to potentially assist viral persistence in the host, eventually leading to hepatocellular carcinoma. The role of HCV on the spontaneous expression of markers suggestive of immune exhaustion and spontaneous apoptosis in immune cells of chronic HCV (CHC) disease largely remain elusive. We investigated the peripheral blood mononuclear cells of CHC patients to determine the spontaneous recruitment of cellular reactive oxygen species (cROS), immunoregulatory and exhaustion markers relative to healthy controls. Using a commercial QuantiGenePlex® 2.0 assay, we determined the spontaneous expression profile of 80 different pro- and anti-apoptotic genes in persistent HCV disease. Onset of spontaneous apoptosis significantly correlated with the up-regulation of cROS, indoleamine 2,3-dioxygenase (IDO), cyclooxygenase-2/prostaglandin H synthase (COX-2/PGHS), Foxp3, Dtx1, Blimp1, Lag3 and Cd160. Besides, spontaneous differential surface protein expression suggestive of T cell inhibition viz., TRAIL, TIM-3, PD-1 and BTLA on CD4+ and CD8+ T cells, and CTLA-4 on CD4+ T cells was also evident. Increased up-regulation of Tnf, Tp73, Casp14, Tnfrsf11b, Bik and Birc8 was observed, whereas FasLG, Fas, Ripk2, Casp3, Dapk1, Tnfrsf21, and Cflar were moderately up-regulated in HCV-infected subjects. Our observation suggests the spontaneous onset of apoptosis signaling and T cell exhaustion in chronic HCV disease.


Hepatitis C virus (HCV) is a serious global health problem which establishes chronic infection in a significant number of infected humans worldwide. IFN and IFN-stimulated genes (ISGs) are amplified during HCV infection but fail to eliminate virus from the liver in a large number of infected patients and the mechanism is not fully understood. MicroRNAs (miRNAs) have been implicated in the control of many biological processes including IFN signaling. To gain more insights on the role of cellular miRNAs in possible counter measures of HCV for suppression of host antiviral response, a miRNA array was performed using primary human hepatocytes (PHH) infected with in vitro cell culture grown HCV. A group of miRNAs were modulated in HCV infected PHH. We focused on miR-373 as this miRNA was significantly upregulated in HCV infected PHH. Here, we analyzed the function of miR-373 in context to HCV infection. HCV infection upregulates miR-373 expression in hepatocytes and HCV infected liver biopsy specimens. Further, we discovered that miR-373 directly targets Janus kinase1 (JAK1) and IFN regulating factor 9 (IRF9), important factors in the IFN signaling pathway. Upregulation of miR-373 by HCV also inhibited STAT1 phosphorylation, which is involved in ISGF3 complex formation and ISGs expression. Knockdown of miR-373 in hepatocytes enhanced JAK1 and IRF9 expression, and reduced HCV RNA replication. Taken together, our results demonstrated
that miR-373 is upregulated during HCV infection and negatively regulated type I IFN signaling pathway by suppressing JAK1 and IRF9. Our results offer a potential therapeutic approach for antiviral intervention. **IMPORTANCE:** Chronic HCV infection is one of the major causes of end stage liver disease worldwide. Although recent introduction of DAA therapy is extremely encouraging, some infected individuals do not respond to this therapy. Further, these drugs target HCV nonstructural proteins and with selective pressure, virus may develop resistant strain. Therefore, understanding the impairment of IFN signals will help in designing additional therapeutic modalities. In this study, we provide evidence of HCV mediated upregulation of miR-373 and show that miR-373 impairs IFN signaling by targeting JAK1/IRF9 molecules. Knockdown of miR-373 inhibited HCV replication by upregulating interferon stimulating genes expression. Together, these results provided new mechanistic insights in understanding the role of miR-373 in HCV infection, and suggest a new potential target against HCV infection.


**AIM:** To study the frequency of vitamin D deficiency in patients with hepatitis C virus (HCV) infection and to evaluate the role of vitamin D supplementation in improving antiviral therapy.

**METHODS:** Sixty-six children aged from 7-14 years (mean ± SD, 11.17 ± 2.293) diagnosed with HCV infection were matched to 28 healthy controls. Serum levels of 25 (OH) D3, calcium, phosphorus, alkaline phosphatase and plasma level of parathormone were measured. Quantitative PCR for HCV was performed Bone density was determined by dual energy X-ray absorptiometry. All cases received conventional therapy, and only 33 patients received vitamin D supplementation. **RESULTS:** Children with HCV showed significantly increased levels of HCV RNA (P < 0.001), parathormone (P < 0.01) and decreased vitamin D levels (P < 0.05) (33.3% deficient and 43.3% insufficient) compared with controls. Abnormal bone status (Z score -1.98 ± 0.75) was found in ribs, L-spine, pelvis and total body. Cases treated with vitamin D showed significant higher early (P < 0.04) and sustained (P < 0.05) virological response. There was a high frequency of vitamin D deficiency among the Egyptian HCV children, with significant decrease in bone density. The vitamin D level should be assessed before the start of antiviral treatment with the correction of any detected deficiency. **CONCLUSION:** Adding vitamin D to conventional Peg/RBV therapy significantly improved the virological response and helped to prevent the risk of emerging bone fragility.


Although it is well established that hepatitis C virus (HCV) entry into hepatocytes depends on clathrin-mediated endocytosis, the possible roles of clathrin in other steps of the viral cycle remain unexplored. Thus, we studied whether cell culture-derived HCV (HCVcc) exocytosis was altered after clathrin interference. Knockdown of clathrin or the clathrin adaptor AP-1 in HCVcc-infected human hepatoma cell cultures impaired viral secretion without altering intracellular HCVcc levels or apolipoprotein B (apoB) and apoE exocytosis. Similar reduction in HCVcc secretion was observed after treatment with specific clathrin and dynamin inhibitors. Furthermore, detergent-free immunoprecipitation assays, neutralization experiments and immunofluorescence analyses suggested that whereas apoE associated with infectious intracellular HCV precursors in endoplasmic reticulum (ER)-related structures, AP-1 participated...
in HCVcc egress in a post-ER compartment. Finally, we observed that clathrin and AP-1 knockdown altered the endosomal distribution of HCV core, reducing and increasing its colocalization with early endosome and lysosome markers, respectively. Our data support a model in which nascent HCV particles associate with apoE in the ER and exit cells following a clathrin-dependent transendosomal secretory route. **IMPORTANCE:** HCV entry into hepatocytes depends on clathrin-mediated endocytosis. Herein, we demonstrate for the first time that clathrin also participates in HCV exit from infected cells. Our data uncover important features of HCV egress, which could lead to the development of new therapeutic interventions. Interestingly, we show that secretion of the VLDL components apoB and apoE is not impaired after clathrin interference. This is a significant finding, since to date it has been proposed that HCV and VLDL follow similar exocytic routes. Given that lipid metabolism has recently emerged as a potential target against HCV infection, our data could help to design new strategies to interfere specifically with HCV exocytosis without perturbing cellular lipid homeostasis, with the aim of achieving more efficient, selective and safe antivirals.

**Adiponectin serum level in chronic hepatitis C infection and therapeutic profile.** Peta V1, Torti C1, Milic N, et al. World J Hepatol. 2015 Jan 27;7(1):44-52. doi: 10.4254/wjh.v7.i1.44. Hepatic steatosis is commonly seen in the patients with chronic hepatitis C virus (HCV) infection. HCV is closely associated with lipid metabolism, and viral steatosis is more common in genotype 3 infection owing to a direct cytopathic effect of HCV core protein. In non-genotype 3 infection, hepatic steatosis is considered largely to be the result of the alterations in host metabolism; metabolic steatosis is primarily linked with HCV genotype 1. Adipose tissue secretes different hormones involved in glucose and lipid metabolisms. It has been demonstrated that adipocytokines are involved in the pathogenesis of non-alcoholic fatty liver disease, as the decreased plasma adiponectin levels, a soluble matrix protein expressed by adipocytes and hepatocyte, are associated with liver steatosis. Various studies have shown that steatosis is strongly correlated negatively with adiponectin in the patients with HCV infection. The role of adiponectin in hepatitis C virus induced steatosis is still not completely understood, but the relationship between adiponectin low levels and liver steatosis is probably due to the ability of adiponectin to protect hepatocytes from triglyceride accumulation by increasing β-oxidation of free fatty acid and thus decreasing de novo free fatty acid production.

**Impaired induction of IL28B and expression of IFNλ4 associated with non-response to interferon-based therapy in chronic hepatitis C.** Murakawa M1, Asahina Y, Nakagawa M, et al. J Gastroenterol Hepatol. 2015 Jan 22. doi: 10.1111/jgh.12902. [Epub ahead of print] **BACKGROUND:** Interferon (IFN) λ plays an important role in innate immunity to protect against hepatitis C viral (HCV) infection. Single nucleotide polymorphisms (SNPs) near IL28B (IFNλ3) are strongly associated with treatment response to IFNα therapy in chronic hepatitis C (CHC) patients. Recently, IFNλ4 related to IL28B-unfavorable allele was discovered. However, the impact of IFNλαs on CHC is unknown. We aimed to investigate the mechanism underlying responsiveness to IFN-based therapy in CHC associated with SNPs near IL28B. **METHODS:** We evaluated the basal mRNA levels and ex-vivo induction of IFNλ expression including IFNλ4 in peripheral blood mononuclear cells (PBMCs) from 50 CHC patients treated with PEG-IFNα/RBV. Furthermore, we investigated the effect of IFNλ4 on induction of IL28B in vitro. **RESULTS:** When PBMCs were stimulated with IFNα and poly(I:C), IL28B induction was significantly lower in patients with IL28B-unfavorable genotype (rs12979860 CT/TT) than those
with IL28B-favorable genotype (rs12979860 CC; p = 0.049). IL28B induction was lower in non-responders than in relapsers (p = 0.04), and it was also lower in non-SVR patients for triple therapy including NS3 protease inhibitors. IFNλ4 mRNA was detected in 12 of 26 patients with IL28B-unfavorable SNP and IFNλ4 expression was associated with lower IL28B induction in patients with IL28B-unfavorable genotype (p = 0.04) and non-response to IFNα therapy (p = 0.003). Overexpression of IFNλ4 suppressed IL28B induction and promoter activation. **CONCLUSIONS:** Impaired induction of IL28B, related to IFNλ4 expression in PBMCs of IL28B-unfavorable patients, is associated with non-response to IFNα-based therapy for HCV infection.

### HIV/HCV Coinfection

**Hepatitis B virus and hepatitis C virus infection among HIV-1-infected injection drug users in Dali, China: prevalence and infection status in a cross-sectional study.** Dong Y1, Qiu C, Xia X, et al. Arch Virol. 2015 Jan 24. [Epub ahead of print].

To assess the prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection and to investigate their mutual influences on infection status among human immunodeficiency virus type 1 (HIV-1)-seropositive injection drug users (IDUs). A cross-sectional study was conducted among HIV infected IDUs in Dali, China. The participants were tested for serological markers of HBV and HCV infection, alanine transaminase (ALT) activity and CD4+ T cell count. HCV genotype was determined by sequencing. Of 529 patients, 498 (94.1 %) HIV infected IDUs agreed to participate. The overall prevalence of HCV infection (anti-HCV antibody positive) and spontaneous HCV clearance were 90.8 % (452/498) and 21.5 % (97/452), respectively. Of 411 subjects who had not received HBV vaccine, 296 (72.0 %) were positive for antibody against HBV core antigen (HBcAb), while 274 (66.7 %) were positive for both HCV antibody and HBcAb. HBV antigens were detected in 52 of the HBV-infected subjects (17.6 %). HCV clearance was associated with HBV antigenemia (p = 0.0002) and higher CD4+ T cell count (p = 0.0294). Resolved HBV infection was associated with HCV genotype 3 (p = 0.0365). HBV and HCV infection are highly prevalent and mutually influence infection status in HIV-1 infected IDUs in Dali, China.


**BACKGROUND:** Chronic hepatitis C virus (HCV) infection is a major cause of morbidity and mortality amongst HIV-infected patients. Sofosbuvir is a first-in-class HCV NS5B inhibitor with potent pan-genotypic antiviral activity. We report a two-part study that assessed the efficacy and safety of sofosbuvir in HCV/HIV co-infected patients. Part A examined potential drug interactions between sofosbuvir and antiretrovirals (efavirenz, emtricitabine, tenofovir, zidovudine, lamivudine, atazanavir, ritonavir, darunavir, and raltegravir). Part B was a pilot study of sofosbuvir plus peginterferon-ribavirin administered for 12 weeks. **METHODS:** Non-cirrhotic patients with chronic HCV infection (genotype 1-6) and stable HIV. Part A followed a five-cohort, open-label, multiple-dose, single-sequence design; Part B followed an open-label, single-arm design. The primary endpoint of Part B was sustained virologic response (defined as undetectable HCV RNA) 12 weeks after end of treatment (SVR12). This study is registered with ClinicalTrials.gov, number NCT01565889. **FINDINGS:** Thirty-eight patients
were enrolled in Part A and 23 in Part B. In Part A, no clinically significant drug interactions were observed between sofosbuvir and any of the antiretrovirals evaluated. In Part B, 21 (91.3%) patients achieved SVR12. Two patients relapsed but none experienced on-treatment HCV virologic failure. Two patients discontinued study treatment because of adverse events (altered mood and anaemia). No serious adverse events, HIV viral breakthrough, or decreases in CD4 percentage were reported in either Part A or Part B. **INTERPRETATION:** Sofosbuvir may be co-administered safely with many commonly used antiretrovirals. The addition of sofosbuvir to peginterferon-ribavirin was highly effective as assessed by SVR in HCV/HIV co-infected patients.

**Therapy with boceprevir or telaprevir in HIV/hepatitis C virus co-infected patients to treat recurrence of hepatitis C virus infection after liver transplantation.** Antonini TM1, Furlan V, Teicher E, et al. AIDS. 2015 Jan 2;29(1):53-8. doi: 10.1097/QAD.0000000000000516.

**OBJECTIVE:** Severe hepatitis C virus (HCV) recurrence affects post-transplant survival in HIV/HCV co-infected patients. This article describes the results of triple anti-HCV therapy with boceprevir or telaprevir in seven HIV/HCV co-infected patients following liver transplantation. **METHODS:** All patients had severe HCV recurrence [fibrosis stage ≥F2 or acute hepatitis ≥A2 (n=5) or fibrosing cholestatic hepatitis (n=2)] associated with genotype 1a (n=4) or 1b (n=3). Patients were treated with Peg-interferon/ribavirin and boceprevir (n=2) or telaprevir (n=5) immediately (n=3) or after a 4-week lead-in phase (n=4). Immunosuppression included either cyclosporine (n=5) or tacrolimus (n=2). Prior to introducing telaprevir, combined antiretroviral therapy was switched in one patient to prevent drug-drug interactions. **RESULTS:** At 24 weeks after the end of treatment, sustained virological response was observed in 60% (3/5) of the patients treated with telaprevir; no responders were observed in the boceprevir group. Triple anti-HCV therapy was prematurely discontinued in six patients [treatment failure (n=2), infection (n=2), acute rejection (n=1) and myocardial infarction (n=1)]. Anaemia occurred in all patients, requiring erythropoietin, ribavirin dose reduction and red blood cell transfusions in five patients. Average cyclosporine doses were reduced by 50-84% after telaprevir initiation and by 33% after boceprevir initiation. Tacrolimus doses were reduced by 95% with telaprevir.

**CONCLUSION:** Our data suggest that in HIV/HCV co-infected patients, triple anti-HCV therapy with telaprevir greatly improved efficacy despite poor tolerability. Significant decreases in cyclosporine or tacrolimus doses are necessary prior to introduction of boceprevir or telaprevir. Close monitoring is essential to prevent drug-drug interactions among antiretroviral therapy, immunosuppressive agents and anti-HCV therapy.


**BACKGROUND AND AIM:** Sofosbuvir-containing regimens have been approved for treatment of HCV in HIV-infected patients. We assessed the effect of treatment with sofosbuvir and ribavirin on patient-reported outcomes (PROs) in HIV/HCV. **METHODS:** HIV/HCV patients were treated with 12 or 24 weeks of sofosbuvir and ribavirin. Matched HCV mono-infected controls were used. All subjects completed standard PRO questionnaires before, during, and post-treatment. **RESULTS:** Included were 497 participants of PHOTON-1, PHOTON-2 clinical trials. At baseline, more impairment in PROs was noted in HIV/HCV co-infected patients compared to HCV mono-infection. During treatment, moderate decrements in PROs (up
to -6.8% on a 0-100% scale, p=0.0053) were experienced regardless of duration, and were similar to those in HCV mono-infection (all p>0.05). In HIV/HCV patients with SVR-12 (N=413), most of PROs improved (up to +7.6%, p<0.0001), also similarly to HCV mono-infected patients. In multivariate analysis, in addition to clinico-demographic predictors, co-infection with HIV was associated with PRO impairment at baseline (up to -7.6%, p<0.002), but not with treatment-emergent changes in PROs (all p>0.05). CONCLUSIONS: Patients with HIV/HCV coinfection tolerate interferon-free sofosbuvir-based anti-HCV regimens well and, despite the presence of some baseline impairment, have similar treatment-emergent changes in PRO scores as compared to those with HCV mono-infection.

Multiple strategies are required to address the information and support needs of gay and bisexual men with hepatitis C in Australia. Hopwood M1, Lea T1, Aggleton P1. J Public Health (Oxf). 2015 Jan 26. pii: fdv002. [Epub ahead of print]

BACKGROUND: Hepatitis C virus (HCV) infection is increasingly reported among gay and bisexual men. However, little is known about the personal and social dimensions of HCV-related experience among these men in Australia. METHODS: An online survey of 474 Australian gay and bisexual men was conducted from August to December 2013. A subsample of 48 HCV mono-infected and HIV/HCV co-infected men was analysed to explore HCV knowledge, sources of information, unmet information needs and use of HCV-related services. RESULTS: More than half of respondents in the subsample were unaware that HIV infection increases the risk of sexually acquired HCV and most wanted information about how to prevent the sexual transmission of HCV. A majority of respondents requested gay-specific HCV services, and approximately similar proportions of men indicated that they would like these services delivered by a hepatitis organization, a lesbian, gay, bisexual, transgender and intersex (LGBTI) organization and a HIV organization. Men in receipt of HIV antiretroviral treatments were most likely to request that gay-specific HCV information and support services be delivered by a LGBTI or HIV organization (OR = 8.63). CONCLUSION: These findings suggest that a variety of organizations are required to address the information and support needs of Australian gay and bisexual men with HCV.


BACKGROUND.: Chronic hepatitis C virus (HCV) infection is a major cause of morbidity and mortality amongst HIV-infected patients. Sofosbuvir is a first-in-class HCV NS5B inhibitor with potent pan-genotypic antiviral activity. We report a two-part study that assessed the efficacy and safety of sofosbuvir in HCV/HIV co-infected patients. Part A examined potential drug interactions between sofosbuvir and antiretrovirals (efavirenz, emtricitabine, tenofovir, zidovudine, lamivudine, atazanavir, ritonavir, darunavir, and raltegravir). Part B was a pilot study of sofosbuvir plus peginterferon-ribavirin administered for 12 weeks. METHODS: Non-cirrhotic patients with chronic HCV infection (genotype 1-6) and stable HIV. Part A followed a five-cohort, open-label, multiple-dose, single-sequence design; Part B followed an open-label, single-arm design. The primary endpoint of Part B was sustained virologic response (defined as undetectable HCV RNA) 12 weeks after end of treatment (SVR12). This study is registered with ClinicalTrials.gov, number NCT01565889. FINDINGS.: Thirty-eight patients were enrolled in Part A and 23 in Part B. In Part A, no clinically significant drug interactions were observed.
between sofosbuvir and any of the antiretrovirals evaluated. In Part B, 21 (91.3%) patients achieved SVR12. Two patients relapsed but none experienced on-treatment HCV virologic failure. Two patients discontinued study treatment because of adverse events (altered mood and anaemia). No serious adverse events, HIV viral breakthrough, or decreases in CD4 percentage were reported in either Part A or Part B. **INTERPRETATION:** Sofosbuvir may be co-administered safely with many commonly used antiretrovirals. The addition of sofosbuvir to peginterferon-ribavirin was highly effective as assessed by SVR in HCV/HIV co-infected patients.

**STARTVerso4: faldaprevir and pegylated interferon α-2a/ribavirin in individuals co-infected with hepatitis C virus genotype-1 and HIV.** Dieterich D1, Nelson M, Soriano V, et al. AIDS. 2015 Jan 21. [Epub ahead of print]

**OBJECTIVE:** Faldaprevir is a potent, once-daily hepatitis C virus (HCV) NS3/4A protease inhibitor. STARTVerso4 assessed the efficacy and safety of faldaprevir and response-guided pegylated interferon α-2a/ribavirin (PegIFN/RBV) in individuals with HCV/HIV co-infection.

**DESIGN:** A phase 3 open-label study (NCT01399619).

**METHODS:** Individuals (N=308) co-infected with HCV genotype 1 (treatment-naïve or prior interferon relapers) and HIV [96% on antiretroviral therapy (ART)] received faldaprevir 120mg (N=123) or 240mg (N=185) and PegIFN/RBV. Those receiving a protease inhibitor or efavirenz ART were assigned to faldaprevir 120 or 240mg, respectively. Individuals achieving early treatment success (ETS; HCV RNA <25IU/ml at week 4 and undetectable at week 8) were randomized to 24 or 48 weeks of PegIFN/RBV. The primary endpoint was sustained virologic response 12 weeks after treatment (SVR12).

**RESULTS:** SVR12 was achieved in 221 (72%) individuals, and the rates were comparable across faldaprevir doses. ETS was achieved in 80%, and of these 86% achieved SVR12, with comparable rates with 24 and 48 weeks of PegIFN/RBV (87 and 94%, respectively). In multivariate analysis, age below 40 years, IL28B CC genotype, and baseline HCV RNA below 800000IU/ml were associated with SVR12 (P=0.027, P<0.0001, and P=0.0002, respectively), whereas treatment (ART regimen and faldaprevir dose), liver cirrhosis, and genotype 1 subtype were not. The safety profile was comparable to that of faldaprevir in HCV-monoinfected individuals.

**CONCLUSIONS:** High SVR12 rates were achieved with faldaprevir and PegIFN/RBV in HIV/HCV co-infected individuals, regardless of faldaprevir dose and background ART, HCV genotype 1 subtype, or cirrhosis status. SVR rates mirrored those obtained with similar regimens in HCV monoinfected individuals.
HCV RNA <25 IU/ml at week 4 and undetectable at week 8) were randomized to 24 or 48 weeks of PegIFN/RBV. The primary endpoint was sustained virologic response 12 weeks after treatment (SVR12). **RESULTS:** SVR12 was achieved in 221 (72%) individuals, and the rates were comparable across faldaprevir doses. ETS was achieved in 80%, and of these 86% achieved SVR12, with comparable rates with 24 and 48 weeks of PegIFN/RBV (87 and 94%, respectively). In multivariate analysis, age below 40 years, IL28B CC genotype, and baseline HCV RNA below 800 000 IU/ml were associated with SVR12 (P = 0.027, P < 0.0001, and P = 0.0002, respectively), whereas treatment (ART regimen and faldaprevir dose), liver cirrhosis, and genotype 1 subtype were not. The safety profile was comparable to that of faldaprevir in HCV-monoinfected individuals. **CONCLUSIONS:** High SVR12 rates were achieved with faldaprevir and PegIFN/RBV in HIV/HCV co-infected individuals, regardless of faldaprevir dose and background ART, HCV genotype 1 subtype, or cirrhosis status. SVR rates mirrored those obtained with similar regimens in HCV monoinfected individuals.


Hepatitis C (HCV) treatment for patients coinfected with human immunodeficiency virus (HIV) and HCV is associated with modest rates of sustained virologic response (SVR) and an increased rate of relapse when compared to HCV monoinfected patients. As patients who attain SVR and patients who relapse are clinically indistinguishable during treatment, where both groups have fully suppressed HCV viral load, it has not been possible to identify in advance those who will relapse. Biomarkers that may distinguish patients with differential treatment response may be clinically useful and provide insight into mechanisms of relapse. In this retrospective study, serum and PBMCs were obtained from 41 HIV/HCV co-infected patients and 17 healthy volunteers. Changes in antibody titers to various regions of the HCV proteome during treatment for HCV were determined using a novel luciferase immunoprecipitation assay. Changes in B-cell subtypes in patients with differential treatment response as well as healthy volunteers were compared. This study demonstrates that elevated anti-HCV core antibody titers persisted during HCV treatment in patients who relapsed when compared to those who attained SVR. Furthermore, characterization of B cells in patients who relapsed demonstrated an abnormal B-cell phenotype distribution characterized by elevated frequencies of exhausted B cells among relapers at baseline, which persisted despite suppression of HCV viremia at 24 weeks, along with increased frequencies of plasmablasts. These data suggest that anti-HCV specific B cells may be responding to ongoing subclinical HCV replication in patients who will relapse.


Hepatitis C virus (HCV) seroprevalence is highly diverse among human immunodeficiency virus-1 (HIV-1) infected patients, ranging between 10% of HIV-1 infected homo-bisexual men, to >92% in patients infected with HIV-1 who acquired HIV-1 through intravenous drug use. Thus, being HCV-free while having acquired HIV-1 via intravenous drug use is a rare situation. Claudin-1 is a protein involved in intracellular tight-junctions and has been identified as a major cellular co-receptor for HCV infection. Our objective was to determine whether Claudin-1 gene (CLDN1) mutations might be involved in natural resistance to HCV infection. We conducted a
case-control study. All recruited patients acquired HIV-1 infection via intravenous drug use route before 1995. The case study patients remained free from HCV infection (negative anti-HCV antibodies and HCV-RNA). The control study patients was co-infected with HCV (positive anti-HCV antibodies). Direct genomic sequencing of the CLDN1 gene coding region and adjacent intron/exons junctions was performed from peripheral blood mononuclear cells. A total of 138 Caucasian patients were enrolled. Twenty-two patients (cases) were free from HCV infection and 116 (controls) were co-infected with HCV. We found single nucleotide polymorphisms (SNPs) described previously with no significant differences in allele frequencies between cases and controls. In conclusion, despite being a major cellular co-receptor for HCV entry in vitro, we did not identify any specific substitution in CLDN1 gene coding region in our study patients highly exposed but resistant to HCV infection in vivo. Other cellular co-factors involved in HCV infection should be investigated in this highly-exposed intravenous drug users patients.

**Epidemiology, Diagnostics, and Miscellaneous Works**


**BACKGROUND:** A sustained viral response (SVR) after interferon-based therapy of chronic hepatitis C virus (HCV) infection is regarded to represent a cure. Previous studies have used different markers to clarify whether an SVR truly represents a cure, but no study has combined a clinical work-up with highly sensitive HCV RNA detection, and the determination of immune responses. **AIM:** To determine clinical, histological, virological and immunological markers 5-20 years after SVR. **METHODS:** In 54 patients, liver biochemistry, histology and elastography were evaluated. Liver biopsies, plasma and peripheral blood mononuclear cells (PBMCs) were tested for minute amounts of HCV RNA. HCV-specific T-cell responses were monitored by ELISpot and pentamer staining, and humoral responses by measuring HCV nonstructural (NS)3-specific antibodies and virus neutralisation. **RESULTS:** Liver disease regressed significantly in all patients, and 51 were HCV RNA-negative in all tissues tested. There was an inverse association between liver disease, HCV-specific T-cell responses and HCV antibody levels with time from SVR, supporting that the virus had been cleared. The three patients, who all lacked signs of liver disease, had HCV RNA in PBMCs 5-9 years after SVR. All three had HCV-specific T cells and NS3 antibodies, but no cross-neutralising antibodies. **CONCLUSIONS:** Our combined data confirm that a SVR corresponds to a long-term clinical cure. The waning immune responses support the disappearance of the antigenic stimulus. Transient HCV RNA traces may be detected in some patients up to 9 years after SVR, but no marker associates this with an increased risk for liver disease.


**OBJECTIVE:** This study examined neurologic abnormalities (as measured by proton magnetic resonance spectroscopy imaging and diffusion tensor imaging), neurocognitive performance, and fatigue among a sample of adults with hepatitis C virus (HCV). We hypothesized that HCV+
individuals would demonstrate structural brain abnormalities and neurocognitive compromise consistent with frontostriatal dysfunction as well as increased fatigue compared to controls. METHOD: Participants were 76 individuals diagnosed with HCV and 20 controls who underwent a comprehensive neurocognitive evaluation and clinical assessments. A subset of the HCV+ participants (n = 29) and all controls underwent MRI. RESULTS: Individuals diagnosed with chronic HCV infection demonstrated greater fractional anisotropy in the striatum as well as greater mean diffusivity in the fronto-occipital fasciculus and external capsule compared to HCV-controls. HCV+ participants also demonstrated lower levels of N-acetylaspartate in bilateral parietal white matter and elevations in myo-inosital (mI) in bilateral frontal white matter compared to HCV- controls (all p values < 0.05). HCV+ participants also demonstrated significantly poorer neuropsychological performance, particularly in processing speed and verbal fluency. HCV+ patients reported higher levels of fatigue than controls, and fatigue was significantly correlated with diffusivity in the superior fronto-occipital fasciculus, elevations in mI in frontal white matter, and overall cognitive performance. CONCLUSIONS: Our results suggest that HCV-associated neurologic complications disrupt frontostriatal structures, which may result in increased fatigue and poorer cognitive performance, particularly in those cognitive domains regulated by frontostriatal regions.

Healthcare Worker Adherence to Follow-up After Occupational Exposure to Blood and Body Fluids at a Teaching Hospital in Brazil. Escudero DV, Furtado GH, Medeiros EA. Ann Occup Hyg. 2015 Jan 30. pii: meu117. [Epub ahead of print] Healthcare workers (HCWs) are at a high risk for exposure to pathogens in the workplace. The objective of this study was to evaluate HCW adherence to follow-up after occupational exposure to blood and body fluids at a tertiary care university hospital in the city of São Paulo, Brazil. Data were collected from 2102 occupational exposures to blood and body fluids reports, obtained from the Infection Control Division of the Universidade Federal de São Paulo/Escola Paulista de Medicina/Hospital São Paulo, in São Paulo, Brazil, occurring between January of 2005 and December of 2011. To evaluate adherence to post-exposure follow-up among the affected HCWs, we took into consideration follow-up visits for serological testing. For HCWs exposed to materials from source patients infected with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV), as well as from source patients of unknown serological status, follow-up serological testing was scheduled for 3 and 6 months after the accident. For those exposed to materials from source patients co-infected with HIV and HCV, follow-up evaluations were scheduled for 3, 6, and 12 months after the accident. During the study period, there were 2056 accidental exposures for which data regarding the serology of the source patient were available. Follow-up evaluation of the affected HCW was recommended in 612 (29.8%) of those incidents. After the implementation of a post-exposure protocol involving telephone calls and official letters mailed to the affected HCW, adherence to follow-up increased significantly, from 30.5 to 54.0% (P = 0.028). Adherence was correlated positively with being female (P = 0.009), with the source of the exposure being known (P = 0.026), with the source patient being HIV positive (P = 0.029), and with the HCW having no history of such accidents (P = 0.047). Adherence to the recommended serological testing was better at the evaluation scheduled for 3 months after the exposure (the initial evaluation) than at those scheduled for 6 and 12 months after the exposure (P = 0.004). During the study period, there was one confirmed case of HCW seroconversion to HCV positivity. The establishment of a protocol that involves the immediate
supervisor of the affected HCWs, in the formal summoning of those HCWs is necessary in order to increase the rate of adherence to post-exposure follow-up.

Among patients newly infected with hepatitis C virus (HCV), only 20-30% clear the infection spontaneously. In the remaining 70% the infection persists, causing chronic liver inflammation and disease. It is well established that polymorphisms in host genes, especially in components of the innate immune response, contribute to the phenomenon of spontaneous HCV clearance. Retinoic acid inducible gene-I (RIG-I)-like helicases such as melanoma differentiation-associated gene 5 (MDA-5) are cytoplasmic sensors of viral RNA that are critical for triggering innate immune responses after infection with RNA viruses. We analyzed 14 nonsynonymous single-nucleotide polymorphisms in RIG-I-like helicase-pathway-genes comparing European patients who spontaneously cleared HCV (n = 285) or had persistent infection (n = 509). We found that polymorphic haplotypes in the MDA-5 gene IFIH1 encoding histidine at position 843 and threonine at position 946 strongly correlate with the resolution of HCV infection (odds ratio [OR]: 16.23; 95% confidence interval [CI]: 3.67-71.87; P = 1.1 × 10(-6) ). Overexpression of MDA-5 genetic variants in HEK 293 cells and in a tissue culture model of HCV infection revealed that the histidine 843/threonine 946 variant leads to increased baseline and ligand-induced expression of interferon-induced genes and confers an increased ability to suppress HCV replication. CONCLUSION: These data suggest that MDA-5 plays a significant role in the defense against HCV and that polymorphisms in MDA-5 can influence the outcome of HCV infection. (Hepatology 2015;61:460-470).

BACKGROUND: Liver disease caused by hepatitis C virus (HCV) is the main indication for liver transplantation (LT) among adults in the US. Recurrent HCV impairs patient and graft survival after LT. The high prevalence of HCV along with scarce organs has lead to increased utilization of HCV+ organs. We estimated the impact of HCV+ donors on patient and graft survival. MATERIAL AND METHODS: We conducted a cohort study of LT recipients age 18 years or older from February 2002 through December 2012 utilizing UNOS data. We evaluated differences in patient characteristics between HCV+ and HCV- recipients. We also compared patient and graft survival between these groups and among HCV+ recipients who received HCV+ versus HCV- donor organs using the Kaplan-Meier estimator and multivariate stratified Cox regression models. RESULTS: We identified 59,899 LT recipients. Among those, 1,695 (2.8%) were HCV+ who received HCV+ grafts. HCV+ recipients of HCV- grafts were more likely to be female, hospitalized, in the ICU, on a ventilator, had higher MELD scores, and higher bilirubin. Patient and graft survival at 1, 5, and 10 years in HCV+ recipients was inferior to HCV- recipients, but HCV+ recipients who received HCV+ versus HCV- grafts were equivalent. Multivariate regression revealed multiple variables associated with worse outcomes. CONCLUSIONS: The use of HCV+ grafts in HCV+ recipients is not associated with worse outcomes. With the increase in HCV+ patients awaiting an organ, more consideration should be given to HCV+ donors.
Inhibition of host-encoded targets, such as the cyclophilins, provides an opportunity to generate potent high barrier to resistance antivirals for the treatment of a broad range of viral diseases. However, many host-targeted agents are natural products, which can be difficult to optimize using synthetic chemistry alone. We describe the orthogonal combination of bioengineering and semisynthetic chemistry to optimize the drug-like properties of sanglifehrin A, a known cyclophilin inhibitor of mixed nonribosomal peptide/polyketide origin, to generate the drug candidate NVP018 (formerly BC556). NVP018 is a potent inhibitor of hepatitis B virus, hepatitis C virus (HCV), and HIV-1 replication, shows minimal inhibition of major drug transporters, and has a high barrier to generation of both HCV and HIV-1 resistance.

Recent studies found that hepatitis C virus (HCV) may invade the central nervous system, and both HCV and Parkinson's disease (PD) have in common the overexpression of inflammatory biomarkers. We analysed data from a community-based integrated screening programme based on a total of 62,276 subjects. We used logistic regression models to investigate association between HCV infection and PD. The neurotoxicity of HCV was evaluated in the midbrain neuron-glia coculture system in rats. The cytokine/chemokine array was performed to measure the differences of amounts of cytokines released from midbrain in the presence and absence of HCV. The crude odds ratios (ORs) for having PD were 0.62 [95% confidence interval (CI), 0.48-0.81] and 1.91 (95% CI, 1.48-2.47) for hepatitis B virus (HBV) and HCV. After controlling for potential confounders, the association between HCV and PD remained statistically significant (adjusted OR = 1.39; 95% CI, 1.07-1.80), but not significantly different between HBV and PD. The HCV induced 60% dopaminergic neuron death in the midbrain neuron-glia coculture system in rats, similar to that of 1-methyl-4-phenylpyridinium (MPP+) but not caused by HBV. This link was further supported by the finding that HCV infection may release the inflammatory cytokines, which may play a role in the pathogenesis of PD. In conclusion, our study demonstrated a significantly positive epidemiological association between HCV infection and PD and corroborated the dopaminergic toxicity of HCV similar to that of MPP+.

Cost-effectiveness of screening for hepatitis C in Canada. Wong WW1, Tu HA1, Feld JJ1, Wong T1, Krahn M1. CMAJ. 2015 Jan 12. pii: cmaj.140711. [Epub ahead of print]
BACKGROUND: The seroprevalence of hepatitis C virus (HCV) infection among Canadians is estimated at 0.3% to 0.9%. Of those with chronic HCV infection, 10% to 20% will experience advanced liver disease by 30 years of infection. Targeted screening seems a plausible strategy. We aimed to estimate the health and economic effects of various screening and treatment strategies for chronic HCV infection in Canada. METHODS: We used a state-transition model to examine the cost-effectiveness of 4 screening strategies: no screening; screen and treat with pegylated interferon plus ribavarin; screen and treat with pegylated interferon and ribavarin-based direct-acting antiviral agents; and screen and treat with interferon-free direct-acting antivirals. We considered Canadian residents in 2 age groups: 25-64 and 45-64 years of age. We
obtained model data from the literature. We predicted deaths related to chronic HCV infection, costs, quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios. **RESULTS:** We found that screening and treating would prevent at least 9 HCV-related deaths per 10,000 persons screened over the lifetime of the cohort. Screening was associated with QALY increases of 0.0032 to 0.0095 and cost increases of $124 to $338 per person, which translated to an incremental cost-effectiveness ratio of $34,359 to $44,034 per QALY gained, relative to no screening, depending on age group screened and antiviral therapy received. **INTERPRETATION:** A selective one-time HCV screening program for people 25-64 or 45-64 years of age in Canada would likely be cost-effective. Identification of silent cases of chronic HCV infection and the offer of treatment when appropriate could extend the lives of Canadians at reasonable cost.


**BACKGROUND:** HCV-TARGET is a longitudinal observational study of chronic hepatitis C virus (HCV) patients treated with direct-acting anti-viral agents (DAAs) in a US consortium of 90 academic and community medical centres. **AIM:** To assess utilisation of response-guided therapy (RGT) and sustained virological response (SVR) of a large cohort of patients. **METHODS:** Patients received peginterferon (PEG-IFN), ribavirin and either telaprevir or boceprevir. Demographical, clinical and virological data were collected during treatment and follow-up. RGT and treatment futility stopping rules was assessed at key time points. **RESULTS:** Of 2,084 patients, 38% had cirrhosis and 56% had received prior treatment for HCV. SVR rates were 31% (95% CI: 24-40) and 50% (95% CI: 44-56) in boceprevir patients with and without cirrhosis, respectively. SVR rates were 46% (95% CI: 42-50) and 60% (95% CI: 57-64) in telaprevir patients with and without cirrhosis, respectively. Early clearance of virus, IL28B genotype, platelet counts and diabetes were identified as predictors of SVR among boceprevir patients, while early clearance of virus, IL28B, cirrhosis, HCV subtype, age, haemoglobin, bilirubin and albumin levels were identified as predictors of SVR for telaprevir patients. **CONCLUSIONS:** In academic and community centres, triple therapy including boceprevir or telaprevir led to SVR rates somewhat lower than those noted in large phase 3 clinical trials. Response rates were consistently higher among patients without cirrhosis compared to those with cirrhosis regardless of DAA used and prior treatment response.


**AIM:** To study the frequency of vitamin D deficiency in patients with hepatitis C virus (HCV) infection and to evaluate the role of vitamin D supplementation in improving antiviral therapy. **METHODS:** Sixty-six children aged from 7-14 years (mean ± SD, 11.17 ± 2.293) diagnosed with HCV infection were matched to 28 healthy controls. Serum levels of 25 (OH) D3, calcium, phosphorus, alkaline phosphatase and plasma level of parathormone were measured. Quantitative PCR for HCV was performed Bone density was determined by dual energy X-ray absorptiometry. All cases received conventional therapy, and only 33 patients received vitamin D supplementation. **RESULTS:** Children with HCV showed significantly increased levels of HCV
RNA (P < 0.001), parathormone (P < 0.01) and decreased vitamin D levels (P < 0.05) (33.3% deficient and 43.3% insufficient) compared with controls. Abnormal bone status (Z score -1.98 ± 0.75) was found in ribs, L-spine, pelvis and total body. Cases treated with vitamin D showed significant higher early (P < 0.04) and sustained (P < 0.05) virological response. There was a high frequency of vitamin D deficiency among the Egyptian HCV children, with significant decrease in bone density. The vitamin D level should be assessed before the start of antiviral treatment with the correction of any detected deficiency. **CONCLUSION:** Adding vitamin D to conventional Peg/RBV therapy significantly improved the virological response and helped to prevent the risk of emerging bone fragility.

**LIVER CANCER**


The function of the novel cell migration-promoting factor, coiled-coil-helix-coiled-coil-helix domain containing 2 (CHCHD2) in liver cancer remains to be elucidated. The aim of the present study was to elucidate the role of CHCHD2 in liver carcinogenesis. Immunohistochemistry was performed on patients with hepatocellular carcinoma (HCC) and suppression subtractive hybridization (SSH) was used for screening differentially expressed genes in the HepG2 cell cDNA library. Chronic hepatitis C virus (HCV) infection frequently leads to liver cancer. The HCV NS2 protein is a hydrophobic transmembrane protein that is associated with certain cellular proteins. Detailed characterization of the nonstructural protein 2 (NS2) of the HCV was performed with respect to its role in transregulatory activity in the HepG2 cell lines. A gel electrophoresis mobility shift assay and a chromatin immunoprecipitation assay were used to confirm the presence of cyclic adenosine monophosphate response element-binding protein (CREB), a transcriptional factor, which specifically interacts with the CHCHD2 promoter. CHCHD2 was highly expressed in the HCC specimens and was consistent with tumor markers of HCC. CHCHD2 was identified by SSH in the HepG2 cells. NS2 upregulated the expression of CHCHD2 by monitoring its promoter activities. The promoter of CHCHD2 contained 350 bp between nucleotides -257 and +93 and was positively regulated by CREB. In conclusion, the results of the present study indicated that CHCHD2 may be a novel biomarker for HCC and that CREB is important in the transcriptional activation of CHCHD2 by HCV NS2.


Nonalcoholic steatohepatitis (NASH) enhances the risk of progressive liver disease. In chronic hepatitis C (CHC), liver steatosis is frequent, especially in genotype 3, but its clinical significance is debated. As squamous cell carcinoma antigen (SCCA)-IgM has been associated with advanced liver disease and risk of tumour development, we evaluated its occurrence in CHC and the possible relation with NASH at liver biopsy. Using a validated ELISA, serum SCCA-IgM was measured in 91 patients with CHC at the time of liver biopsy performed before antiviral treatment, at the end of treatment and 6 months thereafter, and in 93 HCV-negative

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patients with histological diagnosis of nonalcoholic fatty liver disease, as controls. SCCA-IgM was detected in 33% of CHC patients and in 4% of controls. This biomarker was found more elevated in CHC patients with histological NASH, and at multivariate analysis, SCCA-IgM and HCV genotype 3 were independently associated with NASH [OR (95% CI): 6.94 (1.21-40) and 27.02 (4.44-166.6)]. As predictors of NASH, HCV genotype 3 and SCCA-IgM had a specificity and a sensitivity of 97% and 44%, and of 95% and 27%, respectively. PPV and NPV were 80% and 86% for HCV genotype 3 vs 73% and 72% for SCCA-IgM. In patients with sustained virologic response to therapy, SCCA-IgM levels decreased significantly, while these remained unchanged in nonresponders. In conclusion, SCCA-IgM is detectable in one-third of patients with CHC and significantly correlates with histological NASH.


Hepatitis C is a strong prognostic factor for patients with hepatocellular carcinoma (HCC). Although liver resection and liver transplantation offer the chance of a cure for HCC, adequate management of co-existing infection with hepatitis C virus (HCV) is important to enable better long-term outcomes after surgery for HCV-related HCC. For patients undergoing liver resection, perioperative anti-viral treatment is recommended, since a decreased HCV viral load itself is reportedly associated with a lower tumor recurrence rate and a longer overall survival. For patients undergoing transplantaions for HCC complicated by end-stage liver disease, the post-transplant management of HCV infection is also necessary to prevent progressive graft injury caused by active hepatitis under the immunosuppressive condition that is needed after liver transplantation. Although only a few lines of solid evidence are available for postoperative antiviral treatment because of the limited indication and frequent adverse events caused by conventional high-dose combination interferon therapy, new direct acting anti-viral agents would enable interferon-free anti-viral treatment with a higher virologic response and minimal side effects.


The FIB-4 index is a simple formula using age, aspartate aminotransferase, alanine aminotransferase (ALT) and platelet count to evaluate liver fibrosis. We investigated the ability of the FIB-4 index for hepatocarcinogenesis in hepatitis C virus (HCV) carriers with normal ALT levels. A total of 516 patients with ALT levels persistently at or below 40 IU/L during an observation period of over 3 years were included. Factors associated with the development of HCC were determined. Hepatocellular carcinoma (HCC) developed in 60 of 516 patients (11.6%). The incidence rate of HCC at 5 and 10 years was 2.6% and 17.6%, respectively. When patients were categorized according to the FIB-4 index as ≤2.0 (n = 226), >2.0 and ≤4.0 (n = 169), and >4.0 (n = 121), the cumulative incidence of HCC at 5 years was 0.5%, 1.3% and 8.0%, respectively, and 2.8%, 25.6% and 37.1% at 10 years, respectively. Patients with FIB-4 index >4.0 were at the highest risk (P < 0.001). Factors that were significantly associated with HCC in the multivariate analysis were FIB-4 index >2.0 (hazard ratio (HR), 7.690), FIB-4 index >4.0 (HR, 8.991), α-fetoprotein (AFP) >5 ng/mL (HR, 2.742), AFP >10 ng/mL (HR, 4.915) and total bilirubin >1.2 mg/dL (HR, 2.142). A scoring system for hepatocarcinogenesis that combines the
FIB-4 index and AFP predicted patient outcomes with excellent discriminative ability. The FIB-4 index is strongly associated with the risk of HCC in HCV carriers with normal ALT levels.


**INTRODUCTION:** Chronic hepatitis C virus (HCV) infection has recently become a curable disease with antiviral therapy. The knowledge of drug interactions using direct-acting antivirals (DAA) may permit maximizing antiviral efficacy and avoiding drug-related toxicities. Ageing in the chronic hepatitis C population, along with added co-morbidities that require other medications, has increased the attention on drug interactions using DAA. **AREAS COVERED:** This review provides an update of the most clinically significant pharmacokinetic and pharmacodynamic drug interactions occurring between currently available DAA and other medications. The review also revisits how drug interactions with DAA can be prevented and managed. **Expert opinion:** Interactions between DAA and other drugs are frequent in clinical practice. The most frequent drug interactions modify drug metabolism by inducing or inhibiting the cytochrome P450, leading to abnormal drug exposures. Through this mechanism HCV protease inhibitors, especially when co-formulated with ritonavir as pharmacoenhancer, and non-nucleoside HCV polymerase inhibitors interact with other medications. In contrast, NS5B nucleos(t)ide analog inhibitors (i.e., sofosbuvir) and some HCV NS5A inhibitors (i.e., ledipasvir), which do not or only marginally affect CYP450, are relatively free of significant pharmacokinetic interactions. However, exposure to HCV nucleos(t)ide analogs may be influenced by induction/inhibition of drug transporters (i.e., P-glycoprotein) as well as by pharmacodynamic interference with other nucleos(t)ide analogs used as antivirals or cancer drugs. Drug interactions for some NS5A inhibitors (i.e., daclatasvir) are generally moderate and can be managed with dose adjustments.

**Hepatitis C Virus Antibody Prevalence, Demographics and Associated Factors among Persons Screened at Hawai’i Community-based Health Settings, 2010-2013.**
We sought to determine the prevalence of HCV infection and identify factors associated with HCV infection among clients presenting to community-based health settings in Hawai’i from 2010-2013. An earlier report on this study population covered the period from December 2002 through May 2010. Since 2010, the HCV screening inclusion criteria have been relaxed, and the program has greatly expanded. Clients from 26 community-based sites were administered questionnaires, and were screened for HCV antibodies from January 2010 through April 2013 (N = 8,588). Univariate and multivariate logistic regression analyses were performed. HCV antibody prevalence was 5.9% compared with 11.9% from 2002-2010. Persons aged 45-65 years had the highest HCV antibody prevalence (8.4%) compared with all other age groups. Significant independent variables associated with HCV antibody prevalence were injection drug use, blood transfusion before July 1992, and having an HCV-infected sexual partner. While characteristics associated with HCV infection remained essentially unchanged from those identified in the earlier analysis, the expansion of screening sites and less restrictive inclusion criteria led to a much larger study population and a concurrent decrease in overall HCV antibody prevalence. However, while the highest age-specific prevalence remained the same for both screening periods, the prevalence among younger persons (< 30 years old) doubled (from 2.4% to 4.7%). By expanding the HCV screening program and relaxing the inclusion criteria, a greater
number of HCV-infected persons and a greater proportion of younger persons with HCV infection were identified while still maintaining a focus on at-risk individuals.


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The function of the novel cell migration promoting factor, coiled coil helix coiled coil helix domain containing 2 (CHCHD2) in liver cancer remains to be elucidated. The aim of the present study was to elucidate the role of CHCHD2 in liver carcinogenesis. Immunohistochemistry was performed on patients with hepatocellular carcinoma (HCC) and suppression subtractive hybridization (SSH) was used for screening differentially expressed genes in the HepG2 cell cDNA library. Chronic hepatitis C virus (HCV) infection frequently leads to liver cancer. The HCV NS2 protein is a hydrophobic transmembrane protein that is associated with certain cellular proteins. Detailed characterization of the nonstructural protein 2 (NS2) of the HCV was performed with respect to its role in transregulatory activity in the HepG2 cell lines. A gel electrophoresis mobility shift assay and a chromatin immunoprecipitation assay were used to confirm the presence of cyclic adenosine monophosphate response element binding protein (CREB), a transcriptional factor, which specifically interacts with the CHCHD2 promoter. CHCHD2 was highly expressed in the HCC specimens and was consistent with tumor markers of HCC. CHCHD2 was identified by SSH in the HepG2 cells. NS2 upregulated the expression of CHCHD2 by monitoring its promoter activities. The promoter of CHCHD2 contained 350 bp between nucleotides 257 and +93 and was positively regulated by CREB. In conclusion, the results of the present study indicated that CHCHD2 may be a novel biomarker for HCC and that CREB is important in the transcriptional activation of CHCHD2 by HCV NS2.