Directly observed pegylated interferon plus self-administered ribavirin for the treatment of hepatitis C virus infection in people actively using drugs: a randomized controlled trial.

BACKGROUND: This study investigated the efficacy and safety of directly observed pegylated interferon (peg-IFN) alfa-2a plus self-administered ribavirin (RBV) for the treatment of hepatitis C virus (HCV) among people with active drug use. METHODS: A randomized, open-label, parallel group trial of immediate vs delayed treatment with peg-IFN alfa-2a plus RBV in participants with recent injection drug and/or crack cocaine use (prior 3 months). The primary end point was sustained virologic response (SVR). RESULTS: Sixty-six participants were randomized (immediate treatment, n = 48; delayed treatment, n = 18). Loss to follow-up was comparable among those randomized to immediate and delayed treatment (23% vs 33%, P = .389). In a post hoc intent-to-treat analysis of all randomized individuals, the SVR was 65% (95% confidence interval [CI], 49%-78%; 31/48) in those randomized to immediate treatment as compared to 39% (95% CI, 17%-64%; 7/18) in those randomized to delayed treatment (P = .060). Among those who received delayed treatment (12/18), SVR was 58% (7/12). Among 60 participants who received at least 1 dose of study medication, SVR was 63% (95% CI, 50%-75%, n = 38). Recent drug use at baseline (past month) did not impact completion or SVR. Discontinuation due to adverse events occurred in 7%. The HCV reinfection rate was 2.8 per 100 person-years (95% CI, 0.0-14.5 person-years) with 1 reinfection observed among 23 remaining in follow-up post-SVR (median, 1.8 years; range, 0.5-1.8 years). CONCLUSIONS: Among people actively using drugs treated with directly observed peg-IFN alfa-2a plus self-administered RBV, SVR is comparable to that seen in clinical trials of non-drug users, and the rate of HCV reinfection is low.

Effects of Ribavirin Dose Reduction vs Erythropoietin for Boceprevir-Related Anemia in Patients with Chronic HCV Genotype 1 Infection-a Randomized Trial.
BACKGROUND & AIMS: Treatment of Hepatitis C virus (HCV) infection with boceprevir, peginterferon, and ribavirin can lead to anemia, which has been managed by reducing ribavirin dose and/or erythropoietin therapy. We assessed the effects of these anemia management strategies on rates of sustained virologic response (SVR) and safety. METHODS: Patients (n=687) received 4 weeks of peginterferon and ribavirin followed by 24 or 44 weeks of boceprevir (800 mg, 3 times each day) plus peginterferon and ribavirin. Patients who became anemic (levels of hemoglobin approximately ≤10 g/dL) during the study treatment period (n=500) were assigned to groups that were managed by ribavirin dose reduction (n=249) or erythropoietin therapy (n=251). RESULTS: Rates of SVR were comparable between patients whose anemia was managed by ribavirin dose reduction (71.5%) vs erythropoietin therapy (70.9%), regardless of the timing of the first intervention to manage anemia or the magnitude of ribavirin dose reduction. There was a threshold for the effect on rate of SVR: patients who received <50% of the total mg of ribavirin assigned by the protocol had a significantly lower rate of SVR (P<.0001) than those who received ≥50%. Among patients who did not develop anemia, the rate of SVR was 40.1%. Eleven thromboembolic adverse events were reported, in 9 of 295 patients who received erythropoietin, compared to 1 of 392 patients who did not receive erythropoietin. CONCLUSIONS: Reduction of ribavirin dose can be the primary approach for management of anemia in patients receiving peginterferon, ribavirin, and boceprevir for HCV infection. Reduction in ribavirin dose throughout the course of triple therapy does not affect rates of SVR. However, it is important that the patient receives at least 50% of the total amount (mg) of ribavirin assigned by response-guided therapy.

Patterns of Interferon-Alpha-Induced Thyroid Dysfunction Vary with Ethnicity, Sex, Smoking Status, and Pretreatment Thyrotropin in an International Cohort of Patients Treated for Hepatitis C. Mammen JS, Ghazarian SR, Rosen A, Ladenson PW. Thyroid. 2013 Aug 3. [Epub ahead of print]

BACKGROUND: Interferon-alpha (IFNa)–induced thyroid dysfunction occurs in up to 20% of patients undergoing therapy for hepatitis C. The diversity of thyroid disease presentations suggests that several different pathological mechanisms are involved, such as autoimmunity and direct toxicity. Elucidating the relationships between risk factors and disease phenotype provides insight into the mechanisms of disease pathophysiology. METHODS: We studied 869 euthyroid patients from the ACHIEVE 2/3 trial, a randomized international clinical trial comparing pegylated-IFNa2a weekly or albumin-IFNa2b every 2 weeks for up to 24 weeks in patients with hepatitis C, genotype 2 or 3, from 136 centers. The study population was 60% male and 55% white. Serum thyrotropin (TSH) and free thyroxine were measured before therapy, monthly during treatment from week 8, and at 4- and 12-week follow-up visits. RESULTS: Overall, 181 (20.8%) participants had at least one abnormal TSH during the study. Low TSH occurred in 71 (8.2%), of whom 30 (3.5%) had a suppressed TSH below 0.1 mU/L. Hypothyroidism occurred in 53 patients (6.1%), with peak TSH above 10 mU/L in 12 patients (1.4%). Fifty-seven patients had a biphasic thyroiditis (6.6%), with extreme values for the nadir and/or peak TSH in all but one. Medical therapy was given to one thyrotoxic patient, four hypothyroid patients, and 26 biphasic thyroiditis patients. Multivariate logistic regression analysis demonstrated that biphasic thyroiditis is associated with being female and higher pretreatment serum TSH, whereas being Asian or a current smoker decreased the risk of thyroiditis. Hypo- and hyperthyroidism are most strongly predicted by the pretreatment TSH. CONCLUSIONS: Biphasic thyroiditis accounted
for the majority (58%) of clinically relevant IFNα-induced thyroid dysfunction. We confirmed our recent findings in a related cohort that female sex is a risk factor for thyroiditis but not hypothyroidism. Further, in this large multiethnic study, the risk of thyroiditis is dramatically increased, specifically for white women. Smoking was found to be protective of thyroiditis. These results support closer monitoring of women and those with a serum TSH at the extremes of the normal range during therapy so that prompt intervention can mitigate the consequences of thyroid dysfunction associated with IFNα treatment.

**Efficacy of pegylated interferon α-2b and ribavirin in treatment naïve and previously treated children and adolescents with chronic HCV (genotype 1 and 4) infection.**

The course of chronic hepatitis C in children is often mild or asymptomatic, but may lead to liver cirrhosis and neoplasm. The aim of our study was retrospective evaluation of treatment efficacy using pegylated interferon α-2b with ribavirin in children and adolescents with chronic hepatitis C, both treatment naïve and re-treated. The study comprised 79 patients with chronic hepatitis C aged 8 - 18 years (43 patients re-treated; 54 infected with genotype 1 HCV and 25 with genotype 4.), treated with pegylated interferon α-2b (1.5 μg/kg/week) plus ribavirin (15 mg/kg/day) for 48 weeks. The primary endpoint was sustained virologic response (SVR). EVR was observed in 43.1%, ETR in 47.9%. In 44.3% of patients SVR was achieved, which was maintained for at least 6 following months. Patients not treated before significantly more frequently attained EVR, ETR and SVR (64%, 65.6% and 63.9%, respectively) as compared to patients re-treated (30%, 33.3% and 27.9%, respectively). Among 28 patients who attained EVR, 23 achieved SVR. In two patients, despite lack of EVR, SVR was observed. There were numerous side effects. They were not so severe as to discontinue therapy. Combined therapy with pegylated interferon α-2b and ribavirin in patients with chronic hepatitis C, infected with HCV genotype 1 and 4, was more effective in treatment-naïve patients (63.9%) as compared to re-therapy cases (27.9%). SVR was maintained for at least 6 following months in all patients. The applied treatment has limited efficacy and evokes numerous side effects, thus search for new methods of treatment is mandatory.

**The End-of-Treatment Ribavirin Concentration Predicts Hepatitis C Virus Relapse.**

**BACKGROUND:** The optimization of combination therapy with ribavirin (RBV) and pegylated interferon alpha has substantially improved sustained virologic response (SVR) rates and lowered virologic relapse rates in patients infected with hepatitis C virus (HCV). In this study, we performed an analysis of the relationship between the end-of-treatment plasma RBV concentration and virologic relapse. **METHODS:** Thirty-four patients with HCV treated with pegylated interferon/RBV and with an end-of-treatment response were assayed for plasma RBV concentration using liquid chromatography assay coupled to tandem mass-spectrometric detection on the last day of the treatment. Clinical data and the concentration of RBV were compared between patients classified as either relapers or nonrelapers. **RESULTS:** Eleven patients (32.4%) relapsed and 23 patients (67.6%) achieved an SVR. The mean plasma RBV concentration on the last day of treatment was 1380 ± 312 ng/mL for
relapsers and 2278 ± 569 ng/mL for SVR patients (P < 0.0001). A receiver operating characteristic analysis showed that a threshold of 1960 ng/mL was associated with the greatest sensitivity and specificity (100% and 83%, respectively, with an area under the curve of 0.94; P < 0.0001) for discriminating between patients who relapsed and those who did not. A univariate logistic regression analysis indicated that a plasma RBV concentration of <1960 ng/mL at the end of the treatment was strongly associated with relapse (odds ratio, 55; 95% confidence interval, 7.24–∞; P = 0.0001) independently of age, body weight, RBV dose, baseline viral load, the interleukin-28B genotype, and response to previous courses of treatment.

CONCLUSIONS: Our study results highlight the relevance of measuring plasma RBV concentrations during and at the end of HCV treatment, with a view to avoiding virologic relapse.


STUDY OBJECTIVE: To investigate the steady-state pharmacokinetics of methadone when coadministered with ritonavir-boosted danoprevir (DNVr). DESIGN: Open-label, two-period, single-sequence pharmacokinetic study. SETTING: Two U.S. research centers. PATIENTS: Eighteen methadone-maintained healthy adults. MEASUREMENTS AND MAIN RESULTS: In Period 1 (Day -1), subjects received their daily methadone maintenance therapy (MMT). In Period 2 (Days 1-10), subjects received MMT plus DNVr 100/100 mg twice/day. Pharmacokinetic parameters for the total concentrations of (R)- and (S)-methadone on Days -1 and 10 were determined using noncompartmental methods. Unbound (R)- and (S)-methadone concentrations at 3 hours postdose were also assessed on Days -1 and 10. Geometric mean ratios (GMRs) and 90% confidence intervals (CIs) were used to compare steady-state (R)- and (S)-methadone pharmacokinetics when MMT was administered with or without DNVr. Methadone withdrawal was assessed using the Subjective Opiate Withdrawal Scale. Compared with MMT alone, methadone AUCtau and Cmax GMR (90% CI) following coadministration with DNVr were 1.02 (0.91-1.15) and 1.01 (0.90-1.13) for (R)-methadone, and 1.01 (0.90-1.13) and 0.99 (0.89-1.10) for (S)-methadone, respectively. Unbound (R- and (S)-methadone concentrations were comparable with or without DNVr. No instances of methadone withdrawal were reported. MMT in combination with DNVr was well tolerated. CONCLUSION: Coadministration of DNVr with MMT resulted in no significant pharmacokinetic interactions or signs of methadone withdrawal. No dosage adjustment is needed for MMT when coadministered with DNVr.


BACKGROUND: Interferon-free regimens would be a major advance in the treatment of patients with chronic hepatitis C virus (HCV) infection. METHODS: In this phase 2b, randomized, open-label trial of faldaprevir (a protease inhibitor) and deleobuvir (a nonnucleoside polymerase inhibitor), we randomly assigned 362 previously untreated patients with HCV genotype 1 infection to one of five groups: faldaprevir at a dose of 120 mg once daily and deleobuvir at a dose of 600 mg three times daily, plus ribavirin, for 16, 28, or 40 weeks (TID16W, TID28W, or TID40W, respectively); faldaprevir at a dose of 120 mg once daily and
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deleobuvir at a dose of 600 mg twice daily, plus ribavirin, for 28 weeks (BID28W); or faldaprevir at a dose of 120 mg once daily and deleobuvir at a dose of 600 mg three times daily, without ribavirin, for 28 weeks (TID28W-NR). The primary end point was a sustained virologic response 12 weeks after the completion of therapy. **RESULTS:** The primary end point was met in 59% of patients in the TID16W group, 59% of patients in the TID28W group, 52% of patients in the TID40W group, 69% of patients in the BID28W group, and 39% of patients in the TID28W-NR group. The sustained virologic response 12 weeks after the completion of therapy did not differ significantly according to treatment duration or dosage among ribavirin-containing regimens. This response was significantly higher with TID28W than with TID28W-NR (P=0.03). Rates of a sustained virologic response 12 weeks after the completion of therapy were 56 to 85% among patients with genotype 1b infection versus 11 to 47% among patients with genotype 1a infection and 58 to 84% among patients with IL28B CC versus 33 to 64% with non-CC genotypes. Rash, photosensitivity, nausea, vomiting, and diarrhea were the most common adverse events. **CONCLUSIONS:** The rate of a sustained virologic response 12 weeks after the completion of therapy was 52 to 69% among patients who received interferon-free treatment with faldaprevir in combination with deleobuvir plus ribavirin.


**OBJECTIVES:** We evaluated the efficacy of a hepatitis care coordination intervention to improve linkage to hepatitis A virus (HAV) and hepatitis B virus (HBV) vaccination and clinical evaluation of hepatitis C virus (HCV) infection among methadone maintenance patients. **METHODS:** We conducted a randomized controlled trial of 489 participants from methadone maintenance treatment programs in San Francisco, California, and New York City from February 2008 through June 2011. We randomized participants to a control arm (n = 245) and an intervention arm (n = 244), which included on-site screening, motivational-enhanced education and counseling, on-site vaccination, and case management services. **RESULTS:** Compared with the control group, intervention group participants were significantly more likely (odds ratio [OR] = 41.8; 95% confidence interval [CI] = 19.4, 90.0) to receive their first vaccine dose within 30 days and to receive an HCV evaluation within 6 months (OR = 4.10; 95% CI = 2.35, 7.17). A combined intervention adherence outcome that measured adherence to HAV-HBV vaccination, HCV evaluation, or both strongly favored the intervention group (OR = 8.70; 95% CI = 5.56, 13.61). **CONCLUSIONS:** Hepatitis care coordination was efficacious in increasing adherence to HAV-HBV vaccination and HCV clinical evaluation among methadone patients.


**BACKGROUND AND AIM:** It is not yet clear which factors are associated with the outcome of 72-week treatment with pegylated-interferon (PEG-IFN) and ribavirin (RBV) in patients with chronic hepatitis C virus (HCV) infection. **METHODS:** In 66 patients with HCV genotype 1 who had a late viral response (LVR) to 72-week treatment of PEG-IFN and RBV, we examined the factors that determined the outcome, including single nucleotide polymorphisms (SNP) of interleukin-28B (IL28B) and inosine triphosphatase (ITPA) genes. **RESULTS:** Thirty-seven of
66 (56%) patients with LVR achieved a sustained viral response (SVR). The mean age of these 37 SVR patients was 55, compared to 61 in 29 relapsed patients (P = 0.009). Twenty-six of 54 (48%) patients with the CC genotype and 11 of 12 (92%) with the CA/AA genotype of ITPA rs1127354 achieved SVR (P = 0.006). The SVR rates were 79%, 40%, 60% and 33% in patients with undetectable HCV RNA on weeks 16, 20, 24 and 28 or later, respectively (P = 0.014). Finally, serum RBV concentration at week 44 of treatment was significantly higher in the SVR group (2,651 ng/mL) than in the relapse group (1,989 ng/mL, P = 0.002). In contrast, the rate of the IL28B genotype was not different between the groups. Multiple regression analysis showed that age < 60 years, ITPA CA/AA genotype and serum RBV concentration were significant independent predictive factors for SVR. CONCLUSIONS: Our findings elucidated the association of four factors, including ITPA genotype, with the outcome of 72-week treatment in LVR patients.


BACKGROUND & AIMS: IL28B (IFNL3) genotype is the strongest predictor of response of patients with hepatitis C virus (HCV) infection to antiviral therapy. However, patients with HCV infection often have physical or mental comorbidities that contraindicate or complicate treatment, regardless of their genotype. The potential role of IL28B genotype within the context of patients' clinical and social environment is therefore unclear. METHODS: We characterized the IL28B genotype (for rs12980275 and rs8099917) in 308 patients (mean 56 y old; 25% African American; 38% with F3 or F4 stage fibrosis) with genotype 1 HCV infection seen at the Michael E. DeBakey Veterans Administration Medical Center in Houston, Texas from May 1, 2009 through April 1, 2012. We evaluated their eligibility for antiviral treatment, based on clinical and social factors such as physical or mental health comorbidity, ongoing alcohol or drug use, and noncompliance with treatment evaluation. RESULTS: Of the 308 subjects, 40% were homozygous for rs12980275 (associated with response to therapy), 46% were heterozygous, and 15% were homozygous for alleles associated with reduced response to therapy. Overall, 36% of patients were considered to be ineligible for treatment; of these, 40% had the rs12980275 genotype. More than half of the patients with rs12980275 who were ineligible for treatment were excluded because of mental health comorbidities; one-third of these patients had advanced fibrosis. The reason/s for treatment exclusion resolved in only 8% of patients during a mean 1.5 y of follow up. CONCLUSIONS: In a well-characterized cohort of patients with HCV, a large proportion (40%) with IL28B polymorphisms associated with response to therapy is ineligible for treatment because of contra-indications. One potential role of IL28B genotype analysis could be to identify patients who, although not currently eligible for anti-viral treatment, could become so by modifying fixable exclusions to treatment.

Several efforts have been made to establish novel biomarkers with relevant predictive values to monitor HCV-infected patients under peglated Interferon-α2A-(PEG-IFN-α2A)/ribavirin therapy. The aim of this study was to monitor the kinetics of HCV viral load, serum levels of pro-inflammatory/regulatory cytokines and leukocyte activation status before and after PEG-IFN-α2A/ribavirin therapy in 52 volunteers, including 12 chronic HCV patients and 40 controls. The HCV viral load, serum levels of cytokines (IL-8/IL-6/TNF-α/IL-12/IFN-γ/IL-4/IL-10) and the phenotype of peripheral blood leukocytes were evaluated before and after 4, 12 and 24 weeks following the PEG-IFN-α2A/ribavirin therapy. Our results demonstrated that sustained virological response-(SVR) is associated with early decrease in the viral load after 4 weeks of treatment. The presence of a modulated pro-inflammatory profile at baseline favors SVR, whereas a strong inflammatory response at baseline predisposes to therapeutic failure. Furthermore, a time-dependent increase on serum IL-12 levels in patients under treatment is critical to support the SVR, while the early predominance of IL-10 correlates to late virological relapse. On the other hand, a broad but unguided "cytokine storm" is observed in the non-responder HCV patients after 12 weeks of treatment. Corroborating these findings, monocyte/lymphocyte activation at baseline is associated with the non-responders to therapy whereas high CD8+ T-cell numbers associate with SVR. All in all, these data suggest that the baseline pattern of serum pro-inflammatory/regulatory cytokines and the immunological activation status of chronic HCV patients undergoing PEG-IFN-α2A/ribavirin therapy are closely related with the therapeutic response.


PURPOSE: The aim of this study was to characterize the population pharmacokinetics of peginterferon (PEG-IFN) alfa-2b in pediatric patients with chronic hepatitis C and to identify covariates influencing PEG-IFN alfa-2b disposition. METHODS: Pharmacokinetic data from a multicenter open-label study of subcutaneously administered peginterferon alfa-2b (60 μg/m2/wk) plus oral ribavirin (15 mg/kg/day) in patients with chronic hepatitis C aged 3-17 years old was used to develop a population pharmacokinetic nonlinear mixed-effects model. RESULTS: The final population pharmacokinetic analysis was conducted with the pooled data from 107 pediatric patients. A one-compartment model with first-order absorption, first-order elimination, exponential inter-individual variability on clearance, and a combination additive and proportional residual error model adequately described the PEG-IFN alfa-2b pharmacokinetic profile. Age (apparent clearance and apparent volume of distribution) and sex (apparent clearance) were significant covariates. The mean body surface area normalized apparent clearance of PEG-IFN alfa-2b was 0.56 L/h/m2, and was similar when evaluated across the pediatric age groups. CONCLUSION: The final population model suggests age-dependent increases in clearance and volume of distribution of PEG-IFN alfa-2b in pediatric patients with chronic hepatitis C. The apparent clearance normalized to body surface area was similar across pediatric age groups, supporting the use of body size-adjusted dosing in pediatric subjects.

OBJECTIVE: The aim of this study was to determine the serum levels of visfatin, adiponectin, and insulin resistance (IR) in patients with hepatitis C virus (HCV) infection and their relations to the biochemical markers of hepatitis C. MATERIALS AND METHODS: This study was carried out on 40 HCV-infected patients and 40 sex/age/BMI-matched healthy adults. Lipid profile, liver function tests, IR, serum adiponectin, and visfatin of all patients were examined. Correlations between IR, adiponectin, visfatin, and other variables were analyzed. RESULTS: The levels of visfatin and adiponectin were significantly lower in HCV patients compared with healthy controls. However, IR of HCV patients were higher than those of healthy controls. IR was significantly correlated to triglycerides, visfatin was closely related to low-density lipoprotein cholesterol, whereas adiponectin was associated with high-density lipoprotein cholesterol. These results suggest that IR, serum visfatin, and adiponectin levels are associated with metabolic disorders in chronic HCV-infected patients. CONCLUSION: IR, adiponectin, and visfatin were related to several metabolic markers of HCV, suggesting the characteristics of HCV-related metabolic abnormalities.


IMPORTANCE: The efficacy of directly acting antiviral agents in interferon-free regimens for the treatment of chronic hepatitis C infections needs to be evaluated in different populations. OBJECTIVE: To determine the efficacy and safety of sofosbuvir with weight-based or low-dose ribavirin among a population with unfavorable treatment characteristics. DESIGN, SETTING, AND PATIENTS: Single-center, randomized, 2-part, open-label phase 2 study involving 60 treatment-naive patients with hepatitis C virus (HCV) genotype 1 enrolled at the National Institutes of Health (October 2011-April 2012). INTERVENTIONS: In the study's first part, 10 participants with early to moderate liver fibrosis were treated with 400 mg/d of sofosbuvir and weight-based ribavirin for 24 weeks. In the second part, 50 participants with all stages of liver fibrosis were randomized 1:1 to receive 400 mg of sofosbuvir with either weight-based or low-dose 600 mg/d of ribavirin for 24 weeks. MAIN OUTCOMES AND MEASURES: The primary study end point was the proportion of participants with undetectable HCV viral load 24 weeks after treatment completion (sustained virologic response of 24 weeks [SVR24]). RESULTS: In the first part of the study, 9 participants (90%; 95% CI, 55%-100%) achieved SVR24. In the second part, 7 participants (28%) in the weight-based group and 10 (40%) in the low-dose group relapsed after treatment completion leading to SVR24 rates of 68% (95% CI, 46%-85%) in the weight-based group and 48% (95% CI, 28%-69%; P = .20) in the low-dose group. Twenty individuals participated in a pharmacokinetic-viral kinetic substudy, which demonstrated a slower loss rate of infectious virus in relapers than in participants who achieved SVR (clearance, 3.57/d vs 5.60/d; P = .009). The most frequent adverse events were headache, anemia, fatigue, and nausea. There were 7 grade 3 events including anemia, neutropenia, nausea, hypophosphatemia, and cholelithiasis or pancreatitis. No one discontinued treatment due to adverse events. CONCLUSION AND RELEVANCE: In a population of
patients with a high prevalence of unfavorable traditional predictors of treatment response, a 24-week regimen of sofosbuvir and weight-based or low-dose ribavirin resulted in SVR24 rates of 68% and 48%, respectively.


Cryoglobulinemia is characterized by a wide range of causes, symptoms, and outcomes. Hepatitis C virus (HCV) infection is detected in 30%-100% of patients with cryoglobulins. Although more than half the patients with cryoglobulinemic vasculitis present a relatively benign clinical course, some may present with potentially life-threatening situations. We conducted the current study to analyze the clinical characteristics and outcomes of HCV patients presenting with life-threatening cryoglobulinemic vasculitis. We evaluated 181 admissions from 89 HCV patients diagnosed with cryoglobulinemic vasculitis consecutively admitted to our department between 1995 and 2010. In addition, we performed a systematic analysis of cases reported to date through a MEDLINE search. The following organ involvements were considered to be potentially life-threatening in HCV patients with cryoglobulinemic vasculitis: cryoglobulinemic, biopsy-proven glomerulonephritis presenting with renal failure; gastrointestinal vasculitis; pulmonary hemorrhage; central nervous system (CNS) involvement; and myocardial involvement. A total of 279 patients (30 from our department and 249 from the literature search) fulfilled the inclusion criteria: 205 presented with renal failure, 45 with gastrointestinal vasculitis, 38 with CNS involvement, 18 with pulmonary hemorrhage, and 3 with myocardial involvement; 30 patients presented with more than 1 life-threatening cryoglobulinemic manifestation. There were 146 (52%) women and 133 (48%) men, with a mean age at diagnosis of cryoglobulinemia of 54 years (range, 25-87 yr) and a mean age at life-threatening involvement of 55 years (range, 25-87 yr). In 232 (83%) patients, life-threatening involvement was the first clinical manifestation of cryoglobulinemia. Severe involvement appeared a mean of 1.2 years (range, 1-11 yr) after the diagnosis of cryoglobulinemic vasculitis. Patients were followed for a mean of 14 months (range, 3-120 mo) after the diagnosis of life-threatening cryoglobulinemia. Sixty-three patients (22%) died. The main cause of death was sepsis (42%) in patients with glomerulonephritis, and cryoglobulinemic vasculitis itself in patients with gastrointestinal, pulmonary, and CNS involvement (60%, 57%, and 62%, respectively). In conclusion, HCV-related cryoglobulinemia may result in progressive (renal involvement) or acute (pulmonary hemorrhage, gastrointestinal ischemia, CNS involvement) life-threatening organ damage. The mortality rate of these manifestations ranges between 20% and 80%. Unfortunately, this may be the first cryoglobulinemic involvement in almost two-thirds of cases, highlighting the complex management and very elevated mortality of these cases.


**BACKGROUND:** In patients with chronic hepatitis C (CHC), obesity is involved in the pathogenesis of insulin resistance, fatty liver disease and progression of fibrosis. The objective of this study was to compare a normoglucidic low-calorie diet (NGLCD) with a low-fat diet (LFD) among participants with CHC. Aimed to measure the impact of dietary changes in reduction of
insulin resistance, obesity but also in steatosis and fibrosis. **METHODS:** Randomized, controlled trial in three medical centers with assessments at baseline, 6 months and 12 months. Participants were patients over 35 years with chronic hepatitis C (n = 120) with BMI over 25 kg/m². We evaluated the effects of NGLCD vs. LFD in weight management and metabolic improvement. The primary endpoint was to measure the impact of dietary changes through nutritional intervention in reversibility of insulin resistance, obesity, steatosis, and fibrosis. We performed anthropometric measurements, fasting glucose profile, serum lipids, liver profile, blood count at baseline, 6 and 12 months. Steatosis was evaluated using ultrasonographic criteria. Liver fibrosis was non-invasively assessed. **RESULTS:** After 6 and 12 months of intervention, both groups had a significant decrease in caloric consumption. At 6 months, weight loss was greater in the NGLCD group (-5.02 ± 3.43 kg vs. -4.1 ± 2.6 kg; p = 0.002) compared to the LFD group. At 1-year, however, weight loss was similar in both groups (-3.9 ± 3.3 kg vs. -3.1 ± 2.6 kg; p = 0.139). At 12 months, fasting plasma glucose, fasting plasma insulin, and HOMA-IR had significant improvements in both groups. With both diets aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT) decreased with significant differences; also there were significant improvements in AST/ALT ratio, Forns fibrosis index. The two diets were associated with reduction of both the prevalence and the severity of steatosis (all p < 0.001). At 12 months, total cholesterol, HDL-cholesterol, triglycerides improved in both groups (all p < 0.05). **CONCLUSIONS:** The present study establishes the benefits of low-calorie diet and low-fat diet in management of patients with hepatitis C regarding improvement of insulin resistance, steatosis and also fibrosis. Overweight or obese patients with CHC undergoing a lifestyle intervention (specific dietary intervention and physical activity) for 1-year had significant improvements in body weight, lipid and hepatic profile.

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


**BACKGROUND:** Hepatitis C virus (HCV) infection has major health impact worldwide and is a significant cause of chronic liver disease. In Egypt, HCV is highly endemic (up to 15% of the population); 91% of the patients are infected with genotype 4. Searching for new predictors of response to therapy is mandatory to decrease the cost and the adverse effects of current therapy.

**AIM:** The aim of this study was to clarify the usefulness of serum leptin, adiponectin, and insulin resistance (IR) as predictors of response to treatment in hepatitis C virus genotype 4 (HCVG4).

**METHODS:** One hundred patients with chronic HCVG4 who were candidates for treatment with pegylated interferon α and ribavirin were included in the study. Age, sex, and BMI were determined, and quantitative HCV PCR, assessment of serum leptin, adiponectin, IR, and pretreatment liver profile, and liver biopsy were performed. **RESULTS:** The male to female ratio was 68/32; the mean age of the patients was 40.9 ± 7.8 years and BMI was 28.3 ± 10 kg/m². Sustained virological response (SVR) was achieved by 56% of the patients. On performing logistic regression, BMI [odds ratio (OR) 6.5; P=0.004], serum leptin (OR 27.8; P ≤ 0.001), aspartate aminotransferase (OR 1.06; P ≤ 0.001), IR (OR 1.15; P ≤ 0.001), histological activity index (OR 1.77; P=0.006), and fibrosis (OR 2.93; P=0.001) were found to be independent predictors of response to therapy.
negative predictors of SVR, whereas serum adiponectin (OR 0.74; P ≤ 0.001) was found to be an independent positive predictor of SVR. Pretreatment adiponectin (cutoff 13.75; sensitivity 92.86%; specificity 86.86%) shows area under the curve of 0.879 (95% confidence interval 0.802-0.956; P<0.001) and insignificant area under the curve for leptin or IR. CONCLUSION: BMI, pretreatment high leptin levels, and IR are negative predictors for SVR and pretreatment low adiponectin levels are an independent positive predictor for SVR in HCVG4.


GS-9451 is a selective HCV NS3 protease inhibitor in development for the treatment of genotype 1 (GT1) HCV infection. Key preclinical properties of GS-9451 including in vitro antiviral activity, selectivity, cross-resistance, and combination activity as well as pharmacokinetic properties were determined. In multiple GT1a and GT1b replicon cell lines, GS-9451 had mean EC50 values of 13 nM and 5.4 nM, respectively, with minimal cytotoxicity; similar potency was observed in chimeric replicons encoding the NS3 protease gene of GT1 clinical isolates. GS-9451 was less active in GT2a replicon cells (EC50=316 nM). Additive to synergistic in vitro antiviral activity was observed when GS-9451 was combined with other agents including IFN-α, ribavirin, polymerase inhibitors GS-6620 and tegobuvir (GS-9190), as well as the NS5A inhibitor ledipasvir (GS-5885). GS-9451 retained wild-type activity against multiple classes of NS5B and NS5A inhibitor resistance mutations. GS-9451 was stable in hepatic microsomes and hepatocytes from human and three other tested species. Systemic clearance was low in dog and monkey but high in rat. GS-9451 showed good oral bioavailability in all three species tested. In rats, GS-9451 levels were approximately 40-fold higher in liver than plasma after intravenous dosing, and elimination of GS-9451 was primarily through biliary excretion. Together, these results are consistent with the antiviral activity observed in a recent Phase 1b study. Results of in vitro cross-resistance and combination antiviral assays support the ongoing development of GS-9451 in combination with other agents for the treatment of chronic HCV infection.


BACKGROUND & AIMS: HLA-B*27 is associated with spontaneous HCV genotype 1 clearance. HLA-B*27-restricted CD8+ T-cells target three NS5B epitopes. Two of these epitopes are dominantly targeted in the majority of HLA-B*27 patients. In chronic infection, viral escape occurs consistently in these two epitopes. The third epitope (NS5B2820) was dominantly targeted in an acutely infected patient. This was in contrast, however, to the lack of recognition and viral escape in the large majority of HLA-B*27+ patients. Here, we set out to determine the host factors contributing to selective targeting of this epitope. METHODS: Four-digit HLA class I typing and viral sequence analyses were performed in 78 HLA-B*27+ patients with chronic HCV genotype 1 infection. CD8+ T-cell analyses were performed in a subset of patients. In addition, HLA/peptide affinity was compared for HLA-B*27:02 and 05. RESULTS: The NS5B2820 epitope is only restricted by the HLA-B*27 subtype HLA-B*27:02 (that is frequent in Mediterranean populations), but not by the prototype HLA-B*27 subtype B*27:05. Indeed, the
epitope is very dominant in HLA-B*27:02+ patients and is associated with viral escape mutations at the anchor position for HLA-binding in 12 out of 13 HLA-B*27:02+ chronically infected patients. CONCLUSIONS: The NS5B2820 epitope is immunodominant in the context of HLA-B*27:02, but is not restricted by other HLA-B*27 subtypes. This finding suggests an important role of HLA subtypes in the restriction of HCV-specific CD8+ responses. With minor HLA subtypes covering up to 39% of specific populations, these findings may have important implications for the selection of epitopes for global vaccines. (250/250).

Aurintricarboxylic acid (ATA) is a potent inhibitor of many enzymes needed for cell and virus replication, such as polymerases, helicases, nuclease, and topoisomerases. This study examines how ATA interacts with the helicase encoded by the hepatitis C virus (HCV) and reveals that ATA interferes with both nucleic acid and ATP binding to the enzyme. We show that ATA directly binds HCV helicase to prevent the enzyme from interacting with nucleic acids and to modulate the affinity of HCV helicase for ATP, the fuel for helicase action. Amino acid substitutions in the helicase DNA binding cleft or its ATP binding site alter the ability of ATA to disrupt helicase-DNA interactions. These data, along with molecular modeling results, support the notion that an ATA polymer binds between Arg467 and Glu493 to prevent the helicase from binding either ATP or nucleic acids. We also characterize how ATA affects the kinetics of helicase-catalyzed ATP hydrolysis, and thermodynamic parameters describing the direct interaction between HCV helicase and ATA using microcalorimetry. The thermodynamics of ATA binding to HCV helicase reveal that ATA binding does not mimic nucleic acid binding in that ATA binding is driven by a smaller enthalpy change and an increase in entropy.

Hepatitis C virus (HCV) persistence is facilitated by exhaustion of CD8+ T cells that express the inhibitory receptor programmed cell death 1 (PD-1). Blockade of PD-1 signaling improves in vitro proliferation of HCV-specific T lymphocytes, but whether antiviral function can be restored in infected individuals is unknown. To address this question, chimpanzees with persistent HCV infection were treated with anti-PD-1 antibodies. A significant reduction in HCV viremia was observed in one of three treated animals without apparent hepatocellular injury. Viremia rebounded in the responder animal when antibody treatment was discontinued. Control of HCV replication was associated with restoration of intrahepatic CD4+ and CD8+ T-cell immunity against multiple HCV proteins. The responder animal had a history of broader T-cell immunity to multiple HCV proteins than the two chimpanzees that did not respond to PD-1 therapy. The results suggest that successful PD-1 blockade likely requires a critical threshold of preexisting virus-specific T cells in liver and warrants consideration of therapeutic vaccination strategies in combination with PD-1 blockade to broaden narrow responses. Anti-PD-1 immunotherapy may also facilitate control of other persistent viruses, notably the hepatitis B virus where options for long-term control of virus replication are limited.
Gender-related disparities in the regulation of iron metabolism may contribute to the differences exhibited by men and women in the progression of chronic liver diseases associated with reduced hepcidin expression, e.g. chronic hepatitis C, alcoholic liver disease, or hereditary hemochromatosis. However their mechanisms remain poorly understood. In this study, we took advantage of the major differences in hepcidin expression and tissue iron loading observed between Bmp6-deficient male and female mice to investigate the mechanisms underlying this sexual dimorphism. We showed that testosterone robustly represses hepcidin transcription by enhancing Egfr signaling in the liver and that selective Egfr inhibition by gefitinib (Iressa®) in males markedly increases hepcidin expression. In males where the suppressive effects of testosterone and Bmp6-deficiency on hepcidin expression are combined, hepcidin is more strongly repressed than in females and iron accumulates massively not only in the liver but also in the pancreas, heart and kidneys. Conclusion: These data indicate that testosterone-induced repression of hepcidin expression becomes functionally important during homeostatic stress from disorders that result in iron loading and/or reduced capacity for hepcidin synthesis. They suggest that novel therapeutic strategies targeting the testosterone/EGF/EGFR axis may be useful for inducing hepcidin expression in patients with iron overload and/or chronic liver diseases.

BACKGROUND: Genetic variations in interleukin 28B (IL28B) have been strongly associated with a sustained virological response (SVR) in European and African-American patients. Genetic variation of IL28B was investigated in healthy controls and chronic hepatitis C (CHC) patients, and the treatment response in the CHC patients was analyzed according to IL28B polymorphism in the Korean population. METHODS: IL28B polymorphisms (rs12979860 and rs8099917) were studied in 200 healthy controls and in 167 CHC patients who were treated with peginterferon-α and ribavirin. RESULTS: The prevalence of rs12979860 in healthy controls is as follows: the CC-genotype was 88.5%, the CT-genotype was 11.5%, and the TT-genotype was not found. The prevalence of rs8099917 in healthy controls is as follows: the TT-genotype was 89.5%, the TG-genotype was 10.5%, and the GG-genotype was not found. The CC-genotype of rs12979860 and the TT-genotype of rs8099917 were found to be closely related (linkage disequilibrium; D′=1.0, χ²=0.9082). In 106 CHC patients treated with peginterferon and ribavirin, the SVR was 67.2% (n=58) for 1b, 91.6% (n=47) for 2a. In hepatitis C virus (HCV) genotype 1b with respect to rs12979860, the SVR in CC-genotype was 72.9% and that in CT-genotype was 40.0%. On investigating predictive factors for SVR, pretreatment low-HCV RNA levels, HCV genotype non-1, early virological response, and also the IL28B CC-genotype for rs12979860 were good indicators of an SVR. CONCLUSIONS: In Korea, genetic variation of IL28B is different from that in western countries in view of high prevalence of rs12979860 CC-genotype. It seems likely that a high SVR in Korean patients with genotype 1 CHC patients is due to the genetic polymorphism in IL28B.
Kinetic differences in the induction of interferon stimulated genes by interferon-α and IL28B are altered by Infection with Hepatitis C virus.
Several genome-wide association studies (GWAS) have identified a genetic polymorphism associated with the gene locus for interleukin 28B (IL28B), a type III interferon (IFN), as a major predictor of clinical outcome in hepatitis C. Antiviral effects of the type III IFN family have previously been shown against several viruses, including hepatitis C virus (HCV), and resemble the function of type I IFN including utilization of the intracellular JAK-STAT pathway. Effects unique to IL28B that would distinguish it from IFN-α are not well defined. By analyzing the transcriptomes of primary human hepatocytes (PHH) treated with IFN-α or IL28B, we sought to identify functional differences between IFN-α and IL28B to better understand the roles of these cytokines in the innate immune response. Although our data did not reveal distinct gene signatures, we detected striking kinetic differences between IFN-α and IL28B stimulation for interferon stimulated genes (ISGs). While gene induction was rapid and peaked at 8 h of stimulation with IFN-α in PHH, IL28B produced a slower, but more sustained increase in gene expression. We confirmed these findings in the human hepatoma cell line Huh7.5.1. Interestingly, in HCV infected cells, the rapid response after stimulation with IFN-α was blunted, and the induction pattern resembled that caused by IL28B. In conclusion, we describe the kinetics of gene induction as being fundamentally different for stimulations with either IFN-α or IL28B in hepatocytes suggesting distinct roles of these cytokines within the immune response. Furthermore, we demonstrate that the observed differences are substantially altered by infection with the hepatitis C virus.

BACKGROUND & AIMS: Variation of core amino acid (a.a.) 70 of hepatitis C virus (HCV) has been shown recently to be closely correlated with liver disease progression, suggesting that the core region might be present as a quasispecies during persistent infection and this quasispecies nature might have an influence on disease advancement. METHODS: The subjects were 79 patients infected with genotype 1b-HCV (CH, 25; liver cirrhosis (LC), 29; hepatocellular carcinoma (HCC), 25). Deep sequencing of the HCV core region was carried out on their sera using a Roche 454 GS Junior pyrosequencer. RESULTS: Based on a plasmid containing a cloned HCV sequence (pCV-J4L6S), the background error rate associated with pyrosequencing, including the PCR procedure, was calculated as 0.092±0.005/base. Deep sequencing of the core region in the clinical samples showed a mixture of "mutant-type" Q/H and "wild-type" R at core a.a.70 position in most cases (71/79, 89.9 %), and the mixture ratio increased as liver disease advanced to LC and HCC. Meanwhile, phylogenetic analysis of the almost complete core region revealed that the HCV isolates differed genetically depending on the status of the mutation at core a.a.70. CONCLUSIONS: The core a.a. 70 mixture ratio, determined by deep sequencing, reflected the status of liver disease, demonstrating the significant association between core a.a.70 and disease progression in genotype-1b CH-C.

AIM: Insulin resistance (IR) increases during the early stages of hepatitis C virus (HCV)-related chronic liver disease and is a sign of poor prognosis as well as a risk factor for hepatic fibrosis and hepatocellular carcinoma. We aimed to determine the factors affecting IR in HCV-related chronic liver disease. METHODS: We retrospectively examined 71 patients with HCV-related chronic liver disease and analyzed various parameters, including amino acids, as possible predictors of IR. IR was assessed using the Homeostasis Model of Assessment - Insulin Resistance (HOMA-IR). Amino acids were assayed by examining branched-chain amino acids (BCAA), tyrosine level, and the ratio of BCAA to tyrosine level (BTR). RESULTS: HOMA-IR was significantly correlated with body mass index, platelet count, prothrombin time, hemoglobin, total bilirubin, total protein, albumin, total cholesterol, fasting glucose, BTR (r = -0.46, P = 0.0001) and tyrosine (r = 0.55, P < 0.0001). However, BCAA were not significantly correlated with HOMA-IR (r = -0.21, P = 0.082). In multivariate analysis, only two factors were identified as independent parameters contributing to a HOMA-IR of 2.5 or more: total cholesterol (odds ratio [OR], 6.511; 95% confidence interval [95% CI], 1.554-27.284; P = 0.010) and tyrosine (OR, 4.839; 95% CI, 1.087-21.549; P = 0.039). CONCLUSION: Serum tyrosine levels may be associated with IR in patients with HCV-related chronic liver disease.


BACKGROUND: Liver steatosis and iron overload, which are frequently observed in chronic hepatitis C (CHC), may contribute to the progression of liver injury. This study aimed to evaluate the correlation between liver steatosis and iron overload in Polish patients with CHC compared to non-alcoholic fatty liver disease (NAFLD) and HFE-hereditary hemochromatosis (HH) patients. METHODS: A total of 191 CHC patients were compared with 67 NAFLD and 21 HH patients. Liver function tests, serum markers of iron metabolism, cholesterol and triglycerides were assayed. The inflammatory activity, fibrosis, iron deposits and steatosis stages were assessed in liver specimens. HFE gene polymorphisms were investigated by PCR-RFLP. RESULTS: Liver steatosis was associated with obesity and diabetes mellitus. This disease was confirmed in 76/174 (44%) CHC patients, most of whom were infected with genotype 1. The average grade of steatosis was higher in NAFLD patients. CHC patients had significantly higher iron concentrations and transferrin saturations than NAFLD patients. Compared with CHC patients, HH patients had higher values of serum iron parameters and more intensive hepatocyte iron deposits without differences in the prevalence and intensity of liver steatosis. In the CHC group, lipids accumulation in hepatocytes was significantly associated with the presence of serum markers of iron overload. No correlation between the HFE gene polymorphism and liver steatosis in CHC patients was found. CONCLUSIONS: Liver steatosis was diagnosed in nearly half of CHC patients, most of whom were infected with genotype 1. The intensity of steatosis was lower in CHC patients than that in NAFLD patients because of a less frequent diagnosis of metabolic syndrome. Only in CHC patients were biochemical markers of iron accumulation positively correlated with liver steatosis; these findings were independent of HFE gene mutations.

Where active antiretroviral therapy (ART) is accessible, human immunodeficiency virus (HIV) is a survivable illness and effective ART can reduce HIV transmission. Chronic hepatitis C virus (HCV) has emerged as a threat to the survival of individuals harboring both HCV and HIV, due to high prevalence and aggressive disease course. The HCV/HIV coinfection epidemic has been driven by people who inject drugs (PWID), although incident HCV is rising among HIV-infected men who have sex with men in the absence of drug injection. Coinfected individuals warrant aggressive treatment of both viruses; although early ART initiation is recommended to reduce the rate of liver disease progression, the most effective way to decrease HCV-related morbidity and mortality in coinfection is to achieve HCV viral eradication. Direct-acting antiviral (DAA) agents will soon revolutionize HCV treatment. Clinical data are needed regarding the efficacy of DAA in coinfected PWID. Drug-drug interaction studies between ART, DAAs, and opiate substitution therapy must be expedited. Coinfected PWID should have equitable and universal access to HIV/AIDS, HCV, and addiction prevention, care, and treatment. Essential basic steps include improving screening for both infections and engaging coinfected PWID in HIV and HCV care early after diagnoses. Developing strategies to expand access to HCV therapy for coinfected PWID is imperative to stem the HCV epidemic and limit the morbidity and mortality of those at greatest risk for HCV disease progression. The ultimate goal must be the elimination of HCV from all coinfected PWID.


**OBJECTIVE:** To explore the relationship between hepatitis C virus (HCV)/HIV coinfection and responses to initial antiretroviral treatment (ART).

**METHODS:** Four AIDS Clinical Trials Group HIV treatment studies' data were combined to compare initial ART responses between HCV/HIV-coinfected and HIV-monoinfected patients as evaluated by virologic failure, CD4 cell measures, occurrence of AIDS/death and grade 3/4 safety events, using Kaplan-Meier estimates and proportional hazard, regression, and mixed effects models, adjusting for baseline covariates. **RESULTS:** Of the 3041 included participants, 81% were men, 19% had prior history of AIDS, the median (25th, 75th percentile) baseline HIV RNA was 4.72 (4.38-5.18) log10 copies/ml, and the median (25th, 75th percentile) baseline CD4 cell count was 216.0 (76.5-327.0) cells/μl. The 279 HCV/HIV-coinfected individuals were older (44 vs. 37 years), more likely to be black non-Hispanic (47 vs. 36%), and history/current intravenous drug user (52 vs. 5%) than the 2762 HIV-monoinfected patients (all P values <0.001). HCV/HIV coinfection was associated with earlier virologic failure, hazard ratio (95% confidence interval): 1.43 (1.07-1.91); smaller mean CD4 cell increase and CD4% increase [-33.8 (-52.2 to -15.4) cells/μl and -1.16% (-1.43 to -0.89%), respectively] over a median of 132 weeks of follow-up; earlier occurrence of grade 3/4 safety event, hazard ratio 1.51 (1.26-1.81);
and increased AIDS/mortality, hazard ratio 2.10 (1.31-3.37). Treatment effects comparing antiretroviral regimens were not significantly different by HCV/HIV coinfection status.

**CONCLUSION:** HCV/HIV coinfection is associated with attenuated response to ART. Results support earlier initiation of HIV therapy and increased monitoring of those initiating ART with HCV/HIV coinfection.


**BACKGROUND:** Most HIV/HCV-infected patients who are currently receiving boceprevir or telaprevir-based therapy against HCV show cirrhosis. However, the risk of liver decompensations (DC) among HIV/HCV-coinfected patients with stage F3 in the short-term could be high enough to not allow delays. We aimed at assessing the risk of DC among HIV/HCV-coinfected individuals with advanced fibrosis (F3-F4).

**METHODS:** 892 HIV/HCV-coinfected patients, naïve or without SVR to HCV therapy, were included in this cohort. Fibrosis was staged by biopsy in 317 patients and by liver stiffness measurement (LSM) in 575 individuals. LSM 9.5-14.6 KPa was defined as precirrhosis, and ≥14.6 KPa as cirrhosis.

**RESULTS:** For patients with biopsy, the probability of remaining free of DC for F3 vs. F4 was: at 1 year, 99% (95%-100%) vs. 96% (91%-98%); at 3 years, 98% (94%-100%) vs. 87% (81%-92%). The only factor independently associated with DC was fibrosis stage (F4 vs. F3, subhazard ratio [SHR] 2.1; 95%CI, 1.07-4.1; p=0.032). For patients with LSM, the probability of remaining free of DC for precirrhosis vs. cirrhosis was: at 1 year, 99% (96%-100%) vs. 93% (89%-96%); at 3 years, 97% (94%-99%) vs. 83% (77%-87%). Factors independently associated with DC were platelet count (<100x10^3 vs. ≥100x10^3, SHR 1.86; 95%CI, 1.01-3.42; p=0.046) and LSM (cirrhosis vs. precirrhosis, SHR 5.67 (95%CI, 2.27-14.1; p<0.0001).

**CONCLUSIONS:** As in patients with cirrhosis, immediate therapy against HCV is warranted for patients with precirrhosis and HIV coinfection, as they are at risk of DC soon after the diagnosis of advanced fibrosis.


**BACKGROUND & AIMS:** We used longitudinal data from the ANRS CO13 HEPAVIH cohort study of HIV-HCV coinfected individuals to investigate whether polyphenol rich foods intake through coffee and/or daily chocolate consumption could play a role in reducing liver enzymes levels.

**METHODS:** Longitudinal data collection included self-administered questionnaires and medical data (ASpartate aminoTransferase (AST) and ALanine aminoTransferase (ALT) liver enzymes). Two analyses were performed to assess the association between coffee (≥3 cups a day) and daily chocolate intake and abnormal values of AST and ALT (AST or ALT >2.5x upper normal limit (UNL)) (N=990) over time, after adjustment for known correlates. Logistic regression models based on Generalised Estimating Equations were used to take into account the correlations between repeated measures and estimate adjusted odds ratio.

**RESULTS:** After
adjustment, elevated coffee consumption and daily chocolate intake were independently associated with normal ALT (OR = 0.65; p = 0.04 and OR = 0.57; p=0.04, for coffee and chocolate respectively), while only elevated coffee consumption was positively associated with normal AST values (p = 0.05). Nevertheless, the combined indicator of coffee and chocolate intake was most significantly associated with a 40-50% reduced risk of abnormal liver enzymes (p = 0.003 for AST; p = 0.002 for ALT). CONCLUSIONS: Elevated coffee consumption and daily chocolate intake appear to be associated with reduced level of liver enzymes in HIV-HCV co-infected patients. Further experimental and observational research is needed to better understand the role that polyphenol intake or supplementation can play on liver disease and liver injury.


BACKGROUND: Assessing whether hepatitis C (HCV) co-infection with human immunodeficiency virus (HIV) is associated with increased inflammation is complex. The liver, integral to inflammatory biomarker synthesis, is compromised by HCV and alcohol abuse. Using single liver-synthesized biomarkers (e.g. C-reactive protein) to represent inflammation may not be appropriate in HIV/HCV co-infection. We hypothesized that 1) detectable HIV/HCV RNA was independently associated with increased inflammation; 2) a composite inflammation measure describes inflammation differently from single inflammatory biomarkers. METHODS: We compared inflammation by HIV/HCV group in a cohort of 361 HIV infected participants from the HIV-Longitudinal Interrelationships of Viruses and Ethanol study. Inflammatory biomarkers >75th percentile were considered elevated. Associations between HIV/HCV group and elevated biomarkers were analyzed as a composite measure (inflammatory burden) or individually. We defined inflammatory burden as number of concurrently elevated biomarkers. Biomarkers included interleukin-6 (IL-6), C-reactive protein (CRP), cystatin C, serum amyloid-A (SAA), tumor necrosis factor-alpha (TNF-alpha), interleukin-10 (IL-10). Covariates: alcohol, liver fibrosis, comorbidities, CD4 count, antiretroviral therapy, substance use. RESULTS: Detectable HIV and HCV RNA (OR = 2.49; 95%CI = 1.05--5.89) and detectable HCV RNA alone (2.95; 1.08--8.01) were independently associated with increased odds of having a greater inflammatory burden compared to undetectable viremia. Elevated IL-10 (7.79; 1.90--31.97) and TNF-alpha (7.70; 1.42--41.83) were independently associated with detectable HIV and HCV RNA. Elevated IL-10 was also associated with detectable HCV RNA alone (5.51; 1.17, 25.84). CONCLUSIONS: Detectable HIV and HCV replication versus undetectable replication was associated with inflammatory burden and certain inflammatory biomarkers independently of alcohol consumption, liver fibrosis and other comorbidities.


We report, for the first time, the outcome of anti-hepatitis C virus (HCV) triple therapy with telaprevir in an HIV/HCV co-infected transplanted patient. After liver transplantation, the patient experienced a severe HCV recurrence with fibrosing cholestatic hepatitis, and anti-HCV therapy
with pegylated interferon alpha 2a, ribavirin and telaprevir was initiated. A sustained virological response was achieved after 48 weeks of anti-HCV therapy. Drug-drug interactions between antiretroviral therapy, immunosuppressive agents and anti-HCV therapy could be managed.

**COMPLEMENTARY AND ALTERNATIVE MEDICINE**


**ETHNOPHARMACOLOGICAL RELEVANCE:** Hepatocellular carcinoma (HCC) as the major histological subtype of primary liver cancer remains one of the most common malignancies worldwide. Due to the complicated molecular pathogenesis of HCC, the option for effective systemic treatment is quite limited. There exists a critical need to explore and evaluate possible alternative strategies for effective control of HCC. With a long history of clinical use, Chinese herbal medicine (CHM) is emerging as a noticeable choice for its multi-level, multi-target and coordinated intervention effects against HCC. With the aids of phytochemistry and molecular biological approaches, in the past decades many CHM-derived compounds have been carefully studied through both preclinical and clinical researches and have shown great potential in novel anti-HCC natural product development. The present review aimed at providing the most recent developments on anti-HCC compounds derived from CHM, especially their underlying pharmacological mechanisms. **MATERIALS AND METHODS:** A systematic search of anti-HCC compounds from CHM was carried out focusing on literatures published both in English (PubMed, Scopus, Web of Science and Medline) and in Chinese academic databases (Wanfang and CNKI database). **RESULTS:** In this review, we tried to give a timely and comprehensive update about the anti-HCC effects and targets of several representative CHM-derived compounds, namely curcumin, resveratrol, silibinin, berberine, quercetin, tanshinone II-A and celastrol. Their mechanisms of anti-HCC behaviors, potential side effects or toxicity and future research directions were discussed. **CONCLUSION:** Herbal compounds derived from CHM are of much significance in devising new drugs and providing unique ideas for the war against HCC. We propose that these breakthrough findings may have important implications for targeted-HCC therapy and modernization of CHM.

**EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS**


**BACKGROUND:** People who inject drugs (PWID) have a high prevalence of hepatitis C virus (HCV) infection. However, PWID are considered "difficult to treat," requiring a specifically adapted treatment setting, including psychosocial support. **METHODS:** In this prospective, German trial, the impact of psychoeducation (PE) on retention and sustained virologic response (SVR) during HCV therapy among PWID was evaluated. We included 198 patients in opiate substitution therapy, who fulfilled indications for antiviral treatment. All patients received pegylated interferon alfa-2a and ribavirin therapy. Patients in the intervention group (n = 82)
received manualized PE sessions. **RESULTS:** In patients with HCV genotype 1 or 4 (GT 1/4), PE was associated with increased treatment completion (76% vs 55%, P = .038), whereas PE had no such effect among GT 2/3 patients, who showed fewer dropouts and higher SVR rates. Among GT 1/4 patients, a minimum of 5 PE sessions was associated with increased SVR (71% vs 48%, P = .037). Multivariate regression analyses confirmed the impact of PE in GT 1/4 and revealed further predictors for retention and SVR, such as preexisting mental distress and adverse events. **CONCLUSIONS:** In patients with a higher risk of dropout due to GT 1/4 or mental distress, PE was shown to improve retention and SVR. PE is an effective supportive intervention for HCV therapy among PWID.

### The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection.


Although 20%-40% of persons with acute hepatitis C virus (HCV) infection demonstrate spontaneous clearance, the time course and factors associated with clearance remain poorly understood. We investigated the time to spontaneous clearance and predictors among participants with acute HCV using Cox's proportional hazards analyses. Data for this analysis were drawn from an international collaboration of nine prospective cohorts evaluating outcomes after acute HCV infection. Among 632 participants with acute HCV, 35% were female, 82% were Caucasian, 49% had interleukin-28 (IL28)B CC genotype (rs12979860), 96% had injected drugs ever, 47% were infected with HCV genotype 1, and 5% had human immunodeficiency virus (HIV) coinfection. Twenty-eight percent were HCV antibody negative/RNA positive at the time of acute HCV detection (early acute HCV). During follow-up, spontaneous clearance occurred in 173 of 632, and at 1 year after infection, 25% (95% confidence interval [CI]: 21, 29) had cleared virus. Among those with clearance, the median time to clearance was 16.5 weeks (IQR: 10.5, 33.4), with 34%, 67%, and 83% demonstrating clearance at 3, 6, and 12 months. Adjusting for age, factors independently associated with time to spontaneous clearance included female sex (adjusted hazards ratio [AHR]: 2.16; 95% CI: 1.48, 3.18), IL28B CC genotype (versus CT/TT; AHR, 2.26; 95% CI: 1.52, 3.34), and HCV genotype 1 (versus non-genotype 1; AHR: 1.56; 95% CI: 1.06, 2.30). The effect of IL28B genotype and HCV genotype on spontaneous clearance was greater among females, compared to males. Conclusions: Female sex, favorable IL28B genotype, and HCV genotype 1 are independent predictors of spontaneous clearance. Further research is required to elucidate the observed sex-based differences in HCV control.

### Industrial, not Fruit Fructose Intake is Associated with the Severity of Liver Fibrosis in Genotype 1 Chronic Hepatitis C Patients.


**BACKGROUND AND AIMS:** Unhealthy food intake, specifically fructose, has been associated to metabolic alterations and to the severity of liver fibrosis in patients with non-alcoholic fatty liver disease. In a cohort of patients with genotype 1 chronic hepatitis C (G1CHC), we tested the association of fructose intake with the severity of liver histology. **METHODS:** Anthropometric and metabolic factors, including waist circumference(WC), waist-to-hip ratio(WHR), dorso-cervical lipohypertrophy and HOMA were assessed in 147 consecutive biopsy-proven G1CHC patients. Food intake, namely industrial and fruit fructose, was
investigated by a three-day structured interview and a computed database. All biopsies were scored by an experienced pathologist for staging and grading (Scheuer classification), and graded for steatosis, which was considered moderate-severe if $\geq 20\%$. Features of nonalcoholic steatohepatitis (NASH) in CHC were also assessed (Bedossa classification).

**RESULTS:** Mean daily intake of total, industrial and fruit fructose was $18.0 \pm 8.7$ g, $6.0 \pm 4.7$ g, and $11.9 \pm 7.2$ g, respectively. Intake of industrial, not fruit fructose, was independently associated with higher WHR ($p=0.02$) and hypercaloric diet ($p<0.001$). CHC patients with severe liver fibrosis ($\geq F3$) reported a significantly higher intake of total ($20.8 \pm 10.2$ vs. $17.2 \pm 8.1$ g/day; $p=0.04$) and industrial fructose ($7.8 \pm 6.0$ vs. $5.5 \pm 4.2$; $p=0.01$), not fruit fructose ($12.9 \pm 8.0$ vs. $11.6 \pm 7.0$; $p=0.34$). Multivariate logistic regression analysis showed that older age (OR $1.048$, 95%CI $1.004$-$1.094$, $p=0.03$), severe necroinflammatory activity (OR $3.325$, 95%CI $1.347$-$8.209$, $p=0.009$), moderate-severe steatosis (OR $2.421$, 95%CI $1.017$-$6.415$, $p=0.04$), and industrial fructose intake (OR $1.147$, 95%CI $1.047$-$1.257$, $p=0.003$) were independently linked to severe fibrosis. No association was found between fructose intake and liver necroinflammatory activity, steatosis, and the features of NASH.

**CONCLUSIONS:** The daily intake of industrial, not fruit fructose is a risk factor for metabolic alterations and the severity of liver fibrosis in patients with G1CHC.


In the footsteps of groundbreaking achievements made by biomedical research, another scientific revolution is unfolding. Systems biology draws from the chaos and complexity theory and applies computational models to predict emerging behavior of the interactions between genes, gene products, and environmental factors. Adaptation of systems biology to translational and clinical sciences has been termed network medicine, and is likely to change the way we think about preventing, predicting, diagnosing, and treating complex human diseases. Network medicine finds gene-disease associations by analyzing the unparalleled digital information discovered and created by high-throughput technologies (dubbed as "omics" science) and links genetic variance to clinical disease phenotypes through intermediate organizational levels of life such as the epigenome, transcriptome, proteome, and metabolome. Supported by large reference databases, unprecedented data storage capacity, and innovative computational analysis, network medicine is poised to find links between conditions that were thought to be distinct, uncover shared disease mechanisms and key drivers of the pathogenesis, predict individual disease outcomes and trajectories, identify novel therapeutic applications, and help avoid off-target and undesirable drug effects. Recent advances indicate that these perspectives are increasingly within our reach for understanding and managing complex diseases of the digestive system.


**BACKGROUND:** Available data suggest problems in the process of care provided to patients with chronic hepatitis C (HCV). However, the solutions to these problems are less obvious. Healthcare facility factors are potentially modifiable and may enhance process quality in HCV
METHODS: We evaluated the relationship between the process of HCV care and facility factors including number of weekly half-day HCV clinics per 1,000 HCV patients, HCV-specific quality-improvement initiatives, and administrative service of the HCV clinic (gastroenterology, infectious disease, primary care) for a cohort of 34,258 patients who sought care in 126 Veterans Affairs facilities during 2003-2006. We measured HCV care on the basis of 23 HCV-specific process measures capturing pretreatment (seven measures), preventive and/or comorbid (seven measures), and treatment and treatment monitoring care (nine measures).

RESULTS: Patients seen at a facility with >8 half-day clinics were 52 % more likely to receive overall indicated care (OR 1.52, 95 % CI 1.13-2.05). Patients seen at a facility with >3 HCV quality improvement initiatives were more likely to receive better preventive and/or comorbid care (OR 1.32, 95 % CI 1.00-1.74). Compared with patients in facilities with no dedicated HCV clinic, patients at facilities with gastroenterology-based clinics received better pretreatment care (OR 1.36, 95 % CI 1.01-1.85) and more antiviral treatment (OR 1.45, 95 % CI 1.06-1.97) whereas those at facilities with infectious disease-based or primary care-based clinics received better preventive and/or comorbid care (OR 1.59, 95 % CI 1.06-2.39 and 1.84, 95 % CI 1.21-2.79 respectively).

CONCLUSION: Several facility factors affected the process of HCV care. These factors may serve as targets for quality-improvement efforts.


Chronic hepatitis C virus (HCV) infection causes substantial morbidity and mortality in the United States. Testing and treatment of asymptomatic persons might avert progression to more advanced disease. In 1998, CDC published guidelines for HCV testing based on risk factors for infection; however, recent studies indicate that at least one half of all persons living with HCV infection in the United States are unaware of their infection status. To increase testing rates, in 2012 CDC recommended one-time testing of all persons born during 1945-1965. To better understand where and why persons with chronic HCV infection sought their initial testing, 2006-2010 data were analyzed from a survey conducted as part of the ongoing Chronic Hepatitis Cohort Study. Of 4,689 patients with HCV infection who responded to the survey, 60.4% reported that their initial HCV test occurred in a physician's office. CDC's risk-based indications (e.g., injection drug use and hemodialysis) were cited by 1,045 (22.3%) of the patients as reasons for testing, whereas clinical indications (e.g., abnormal liver function tests or liver-related symptoms such as jaundice) were cited by 2,121 (45.2%), suggesting that many HCV infections were identified only after the patient had become symptomatic. Promoting U. S. Preventive Services Task Force and CDC recommendations for testing and identifying strategies that help physicians implement HCV testing in their offices might help facilitate timely identification of HCV infection and reduce morbidity and mortality.


BACKGROUND: No systematic attempts have been made to estimate the global and regional prevalence of amphetamine, cannabis, cocaine, and opioid dependence, and quantify their...
burden. We aimed to assess the prevalence and burden of drug dependence, as measured in years of life lived with disability (YLDs), years of life lost (YLLs), and disability-adjusted life years (DALYs). **METHODS:** We conducted systematic reviews of the epidemiology of drug dependence, and analysed results with Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010) Bayesian meta-regression technique (DisMod-MR) to estimate population-level prevalence of dependence and use. GBD 2010 calculated new disability weights by use of representative community surveys and an internet-based survey. We combined estimates of dependence with disability weights to calculate prevalent YLDs, YLLs, and DALYs, and estimated YLDs, YLLs, and DALYs attributable to drug use as a risk factor for other health outcomes. **FINDINGS:** Illicit drug dependence directly accounted for 20.0 million DALYs (95% UI 15.3-25.4 million) in 2010, accounting for 0.8% (0.6-1.0) of global all-cause DALYs. Worldwide, more people were dependent on opioids and amphetamines than other drugs. Opioid dependence was the largest contributor to the direct burden of DALYs (9.2 million, 95% UI 7.1-11.4). The proportion of all-cause DALYs attributed to drug dependence was 20 times higher in some regions than others, with an increased proportion of burden in countries with the highest incomes. Injecting drug use as a risk factor for HIV accounted for 2.1 million DALYs (95% UI 1.1-3.6 million) and as a risk factor for hepatitis C accounted for 502 000 DALYs (286 000-891 000). Suicide as a risk of amphetamine dependence accounted for 854 000 DALYs (291 000-1 791 000), as a risk of opioid dependence for 671 000 DALYs (329 000-1 730 000), and as a risk of cocaine dependence for 324 000 DALYs (109 000-682 000). Countries with the highest rate of burden (>650 DALYs per 100 000 population) included the USA, UK, Russia, and Australia. **INTERPRETATION:** Illicit drug use is an important contributor to the global burden of disease. Efficient strategies to reduce disease burden of opioid dependence and injecting drug use, such as delivery of opioid substitution treatment and needle and syringe programmes, are needed to reduce this burden at a population scale. **FUNDING:** Australian National Health and Medical Research Council, Australian Government Department of Health and Ageing, Bill & Melinda Gates Foundation.


**BACKGROUND:** The effect of anti-viral treatment on downstream costs for hepatitis C virus (HCV)-infected patients is unknown. **AIM:** To evaluate follow-up costs in patients with chronic HCV, stratified by liver disease severity. **METHODS:** Using a US private insurance database, mean all-cause per-patient-per-month (PPPM) US (2010) medical costs were calculated for HCV-infected persons who did and did not receive anti-HCV treatment between January 2002 and August 2010. Analysis was stratified by liver disease severity [noncirrhotic disease (NCD), compensated cirrhosis (CC) or end-stage liver disease (ESLD)] defined by ICD-9 and CPT codes. **RESULTS:** A total of 33 309 patients were included (78% NCD, 7% CC and 15% ESLD); 4111 individuals (12%) received anti-HCV treatment during the 2-year baseline period. Mean PPPM follow-up health care costs were significantly lower among treated patients with NCD ($900 vs. $1378 in untreated patients, P < 0.001) and ESLD ($3634 vs. $5071, P < 0.001) groups but not in the CC group ($1404 vs. $1795, P < 0.071; t-test). In a multivariable model adjusted for demographic characteristics, comorbidities, index date and geographical region,
incremental cost ratios for total health care costs differed significantly (P < 0.001) between treated and untreated patients in the NCD and ESLD groups but not in the CC group. From this model, mean PPPM total health care costs between treated and untreated patients were $885 and $1370 in the NCD, $1369 and $1802 in the CC, and $3547 and $5137 in the ESLD groups, respectively. **CONCLUSIONS:** Anti-HCV therapy was associated with lower follow-up US health care costs, and these savings were independent of baseline patient comorbidities and stage of disease.


Psychiatric comorbidity is a common problem in patients with substance use disorders. Patients with psychiatric diseases and/or substance abuse have an increased risk for hepatitis C virus (HCV) infection. Furthermore, psychiatric problems occur frequently during antiviral treatment and may be associated with the use of interferon alpha (IFN-α) but also with the primary psychiatric condition. As a consequence, substance abuse and/or acute psychiatric problems are still important reasons for nontreatment of chronic HCV infection. However, prospective and controlled data from recent years showed that if an interdisciplinary treatment is provided, patients with substance use disorders and/or psychiatric diseases do not differ regarding sustained virologic response or IFN-α-associated complications such as depression when compared with controls. Moreover, depression as the most important acute IFN-α-associated psychiatric adverse event can be acutely treated or even prevented by antidepressant pretreatment. Other, more rare but severe complications such as mania, psychotic symptoms, or delirium need individual psychiatric interventions.

**LIVER CANCER**


Sorafenib (SO) was the first targeted agent to produce significant improvements in overall survival in patients with advanced hepatocellular carcinoma (HCC). We report the case of a cirrhotic patient with chronic hepatitis C virus infection; locally advanced, unresectable, multinodular HCC, and portal vein tumor thrombosis, who achieved complete tumor regression following SO treatment. The patient was treated with SO 400 mg twice daily, which was subsequently reduced to 200 mg twice daily due to the occurrence of hand-foot skin reaction. The patient also received the following concomitant medications: Synchro-Levels® (Alphrema, Varese, Italy), silymarin and vitamin E. Long-term treatment with reduced SO dosage and Synchro-Levels resulted in a sustained radiological and clinical response with normalization of α-fetoprotein levels. Observed side effects were mostly low grade and manageable following dose adjustments. After 44 months of treatment the patient was in good physical condition, which suggests that a complete response with long-term SO is achievable in patients with locally advanced HCC.

Hepatocellular carcinoma (HCC) is the fifth most common form of cancer globally and is rarely curable once detected. The 5-year survival rate of patients diagnosed with late-stage HCC may be as low as 27%. HCC is a cancer largely driven by epigenetic changes that arise from exposure to exogenous environmental factors rather than coding sequence mutations. The liver is susceptible to effects from Hepatitis C and Hepatitis B viruses, exposure to aflatoxin and continuous excessive consumption of alcohol. The liver is a highly metabolic organ balancing many vital biochemical processes; exposure to any of the above environmental factors is associated with loss of liver function and is a major risk factor for the development of HCC. Emerging studies aim to examine the underlying metabolic processes that are abrogated in cancer and lead to the altered flux and availability of key metabolites important for epigenetic processes. Metabolites have been shown to act as substrates for many canonical epigenetic regulators. These enzymes are responsible for regulating histone modification, DNA methylation and micro RNA expression. By studying the impact of altered liver metabolism, we may better understand the long-term epigenetic processes, which lead to the development and progression of HCC.


In this article, we present a study on the levels of epidermal growth factor (EGF), its phosphorylated receptor (p-EGFR) and transforming growth factor-β1 (TGF-β1) in the sera of patients with hepatocellular carcinoma (HCC) and chronic hepatitis C (CHC) infection. The results reveal significant higher serum levels of EGF and TGF-β1 in patients with HCC compared to their level in patients with CHC infection and control subjects. The levels of p-EGFR in HCC and CHC patients show a highly significant difference between patients. Based on the best cutoff value of 914 pg/ml, EGF shows 63.3 % sensitivity and 87.5 % specificity for HCC patients where the area under the curve is 0.81. The p-EGFR shows sensitivity of 63.3 % and specificity of 100 % where the area under the curve is 0.87 for HCC patients based on the best cutoff value of 39 U/mg protein. The best cutoff value (370 pg/ml) for serum TGF-β1 displays sensitivity of 86.7 % and specificity of 100 %, where the area under the curve is 0.97 for HCC patients.


Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. Most HCCs develop in cirrhotic livers. Alcoholic liver disease, chronic hepatitis B and chronic hepatitis C are the most common underlying liver diseases. Hepatitis C virus (HCV)-specific mechanisms that contribute to HCC are presently unknown. Transgenic expression of HCV proteins in the mouse liver induces an overexpression of the protein phosphatase 2A catalytic subunit (PP2Ac). We have previously reported that HCV-induced PP2Ac overexpression modulates histone
methylation and acetylation and inhibits DNA damage repair. In this study, we analyze tumor formation and gene expression using HCV transgenic mice that overexpress PP2Ac and liver tissues from patients with HCC. We demonstrate that PP2Ac overexpression interferes with p53-induced apoptosis. Injection of the carcinogen, diethylnitrosamine, induced significantly more and larger liver tumors in HCV transgenic mice that overexpress PP2Ac compared with control mice. In human liver biopsies from patients with HCC, PP2Ac expression was significantly higher in HCC tissue compared with non-tumorous liver tissue from the same patients. Our findings demonstrate an important role of PP2Ac overexpression in liver carcinogenesis and provide insights into the molecular pathogenesis of HCV-induced HCC.


Primary liver cancer is a global disease that is on the increase. Hepatocellular carcinoma (HCC) accounts for most primary liver cancers and has a notably low survival rate, largely attributable to late diagnosis, resistance to treatment, tumour recurrence and metastasis. MicroRNAs (miRNAs/miRs) are regulatory RNAs that modulate protein synthesis. miRNAs are involved in several biological and pathological processes including the development and progression of HCC. Given the poor outcomes with current HCC treatments, miRNAs represent an important new target for therapeutic intervention. Several studies have demonstrated their role in HCC development and progression. While many risk factors underlie the development of HCC, one process commonly altered is iron homeostasis. Iron overload occurs in several liver diseases associated with the development of HCC including Hepatitis C infection and the importance of miRNAs in iron homeostasis and hepatic iron overload is well characterised. Aberrant miRNA expression in hepatic fibrosis and injury response have been reported, as have dysregulated miRNA expression patterns affecting cell cycle progression, evasion of apoptosis, invasion and metastasis. In 2009, miR-26a delivery was shown to prevent HCC progression, highlighting its therapeutic potential. Several studies have since investigated the clinical potential of other miRNAs with one drug, Miravirsen, currently in phase II clinical trials. miRNAs also have potential as biomarkers for the diagnosis of HCC and to evaluate treatment efficacy. Ongoing studies and clinical trials suggest miRNA-based treatments and diagnostic methods will have novel clinical applications for HCC in the coming years, yielding improved HCC survival rates and patient outcomes.


**BACKGROUND:** Hepatocellular carcinoma (HCC) incidence is rising in the United States. Hepatitis B virus (HBV) and hepatitis C virus (HCV) are major causes of HCC. Hepatitis infection in HCC patients is generally diagnosed by serology, which is not always consistent with the presence of HBV and HCV in the liver. The relationship of liver viral status to serostatus in hepatocarcinogenesis is not fully understood. **METHODS:** HBV and HCV were evaluated in formalin-fixed paraffin-embedded liver tissue specimens in a retrospective study of 61 U.S. HCC cases of known serologic status. HBV DNA and HCV RNA were detected by PCR, RT-PCR and pyrosequencing, and HBsAg and HBeAg were evaluated by
immunohistochemistry. **RESULTS:** Viral markers were detected in the liver tissue of 25 of 61 (41%) HCC cases. Tissue viral and serologic status were discordant in 27 (44%) cases, including those with apparent "occult" infection. Specifically, HBV DNA was detected in tissue of 4 of 39 (10%) serum HBsAg (-) cases, including 1 anti-HCV(+) case; and HCV RNA was detected in tissue of 3 of 42 (7%) anti-HCV seronegative cases, including 2 with serologic evidence of HBV. **CONCLUSIONS:** Viral hepatitis, including HBV-HCV coinfection, may be unrecognized in up to 17% of HCC patients when based on serology alone. Further research is needed to understand the clinical significance of viral markers in liver tissue of HCC patients in the absence of serologic indices. Impact. The contribution of HBV and HCV to the rising incidence of HCC in the United States may be underestimated.


Although overt hepatitis B virus (HBV) infection promotes the onset of hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients, the effect of occult HBV infection remains unclear. The aim of this study was to investigate the effect of occult HBV infection on the early-onset of HCC in HCV-infected patients. A total of 173 HCC patients with HCV infection were enrolled and classified into 2 groups according to the median age of HCC onset: the early-onset group (n=91; 61.1±5.6 years) and the late-onset group (n=82; 73.8±3.7 years). Independent factors associated with the early-onset of HCC were assessed by multivariate analysis. In the overall analysis, independent risk factors for the early-onset of HCC were the white blood cell count and alanine aminotransferase level, but not the presence of HBV DNA. In a stratification analysis according to albumin levels of ≥3.5 g/dl, the presence of HBV DNA was a significant independent risk factor for the early-onset of HCC (OR 145.18, 95% CI 1.38-15296.61, P=0.036), whereas the presence of antibodies against hepatitis B core antigen was not found to be a risk factor. The presence of HBV DNA was not a risk factor for the early-onset of HCC in the overall analysis. However, its presence was an independent factor for the early-onset of HCC in HCV-infected patients with an albumin level of ≥3.5 g/dl. Thus, occult HBV infection may accelerate hepatocarcino-genesis in HCV-infected patients with relatively low carcinogenic potential.


**BACKGROUND:** Hepatocellular cancer (HCC) commonly complicates chronic liver disease and increases in incidence have been reported despite falling prevalences of viral hepatitis. **METHODS:** Following the introduction of centralised specialist teams to manage patients with cancer in England, we characterised the demographics of patients with HCC referred to the Newcastle-upon-Tyne Hospitals NHS Foundation Trust between 2000 and 2010. Regional HCC mortality data was from Public Health England. **RESULTS:** HCC related mortality in the region rose 1.8 fold in 10 years, from 2.0 to 3.7 per 100,000. 632 cases were reviewed centrally, with 2-3 fold increases in referrals of patients with associated hepatitis C, alcoholic liver disease or no chronic liver disease and a >10 fold increase in HCC associated with non-alcoholic fatty liver disease (NAFLD). By 2010 NAFLD accounted for 41/118 (34.8%) cases. Irrespective of
associated etiologies, metabolic risk factors were present in 78/118 (66.1%) cases in 2010, associated with regional increases in obesity and diabetes. Median overall survival was just 10.7 months. Although patients with NAFLD associated HCC were older (71.3yrs versus 67.1yrs; p<0.001) and their cancers less often detected by surveillance, their survival was similar to other etiologies. This was attributed to significantly higher incidental presentation (38.2%) and lower prevalence of cirrhosis (77.2%). CONCLUSION: HCC related mortality is increasing, with typical patients being elderly with metabolic risk factors. The prognosis for most is poor, but older patients with co-morbidities can do well managed within a specialist multidisciplinary team if their cancer is detected pre-symptomatically.


Hepatocellular carcinoma (HCC) is the third most common cause of death from cancer. The incidence and mortality of HCC are increasing in most Western countries as a result of an ageing cohort infected with chronic hepatitis C, and are expected to continue to rise as a consequence of the obesity epidemic. Chemopreventive strategies aimed at decreasing the risk or delaying the onset of HCC are needed. Universal immunization against HBV and antiviral therapy against HBV and HCV in patients with established disease has consistently been associated with reduced HCC risk, especially in patients who achieve sustained virologic response. However, the cost-effectiveness of antiviral therapy for primary HCC prevention is not known. Several commonly prescribed medications seem promising as chemopreventive agents against HCC, including statins, antidiabetic medications and aspirin. Dietary agents such as coffee, vitamin E and fish oil as well as phytochemicals might also be associated with reduced risk of HCC. Though randomized controlled trials are ideally needed to firmly establish efficacy, such chemoprevention trials are logistically and ethically challenging. Well-designed, prospective, population-based cohort studies might provide the best evidence for chemopreventive efficacy of these agents.


PURPOSE: We evaluated the impact of the Killer Immunoglobulin-like Receptors (KIRs) of natural killer (NK) cells and of their Human Leukocyte Antigen (HLA) ligands over the clinical outcome of HCV-related hepatocellular carcinoma (HCC) after curative treatment by either surgical resection (SR) or radiofrequency thermal ablation (RTA).

EXPERIMENTAL DESIGN: Sixty-one consecutive patients with HCV-related HCC underwent KIR genotyping and HLA typing. A phenotypic/functional characterization of NK-cells was carried out in patients with different KIR/KIR-ligand genotype. RESULTS: Activating KIR2DS5 was associated with significantly longer time to recurrence (TTR) and overall survival (OS) (p<0.03 each). Homozygous HLA-C1 (p<0.02) and HLA-Bw4I80 (p<0.05) were expressed by patients with significantly better OS, while HLA-C2 (p<0.02) and HLA-Bw4T80 (p<0.01) were associated with a worse OS. Multivariate analysis identified as parameters independently related to TTR the type of treatment (SR vs RTA) (p<0.03) and HLA-C1 (p<0.03), whereas only KIR2DS5 was an independent predictor of longer OS (p<0.05). Compound KIR2DL2-C1 and
KIR3DS1-Bw4T80 genotypes were associated with better TTR (p<0.03) and worse OS (p=0.02), respectively. A prevalent cytotoxic (CD56dim) NK phenotype was detected in patients with both longer TTR and OS. Cytotoxic capacity measured by upregulation of CD107a was significantly higher in subjects with HLA-C1 alone or combined with KIR2DL2/KIR2DL3. CONCLUSIONS: These results support a central role of NK-cells in the immune response against HCC, providing a strong rationale for therapeutic strategies enhancing NK response and for individualized post-treatment monitoring schemes.


**http://www.ncbi.nlm.nih.gov/pubmed/23432377**

**BACKGROUND AND AIM:** Follistatin (FST) is a glycoprotein expressed in most organs, which interacts with activins or other members of the transforming growth factor beta family. Recently, several reports have shown that FST regulates a variety of processes during tumor progression. Here, serum FST in patients with liver diseases was measured, and its clinical utility as a biomarker was assessed. **METHODS:** Serum was collected from 162 patients (91 hepatocellular carcinoma [HCC], 43 liver cirrhosis, and 28 chronic hepatitis) as well as from 16 healthy volunteers. FST was quantified by enzyme-linked immunosorbent assays, and levels were compared with clinical parameters including survival of the HCC patients. **RESULTS:** Median serum FST levels in HCC, liver cirrhosis, chronic hepatitis, and healthy volunteers were 1168, 1606, 1324, and 1661 pg/mL, respectively, not significantly different. In HCC patients, higher serum FST was associated with greater age, hepatitis C virus antibody-negativity, large tumor size, g-glutamyl transpeptidase, des-gamma carboxyprothrombin and presence of portal vein tumor thrombus. Survival of HCC patients with high FST levels was significantly shorter than for those with low levels (P = 0.004). Multivariate analysis revealed that in addition to large tumor size and presence of portal vein thrombus, high FST levels were independently correlated with poor prognosis (hazard ratio = 2.41, 95% confidence interval = 1.16-5.00, P = 0.02). **CONCLUSIONS:** Serum FST levels are significantly associated with HCC prognosis and could represent a predictive biomarker in this disease.