
GOALS AND BACKGROUND: Besides United States population born between 1945 and 1965, screening for hepatitis C virus (HCV) is not recommended for the general US population. However, HCV may be more prevalent in certain subgroups and screening may be warranted. The goal of this study was to examine the proportion of HCV in a large sample of community Asian American patients presenting for non-liver-related complaints. STUDY: We conducted a cross-sectional study of 1246 patients tested for hepatitis C virus antibodies (anti-HCV) referred to 2 gastroenterology clinics for non-liver-related gastrointestinal reasons between January 2001 and February 2011. We determined HCV status and patient history via electronic medical record review. RESULTS: Of the 1246 study patients tested for anti-HCV, the majority were Asian (81.4%) and 29 Asian patients (2.9%) had positive anti-HCV. HCV proportion in the remaining 232 non-Asians (non-Hispanic whites and Hispanics) was 1.7%. Asians with positive anti-HCV were more likely to have had blood transfusions (31.0% vs. 6.6%, P<0.0001) or acupuncture (10.3% vs. 1.5%, P<0.0001). Of the 976 Asian patients with hepatitis B surface antigen testing, 38 (3.9%) also had detectable hepatitis B surface antigen. CONCLUSIONS: Among patients seen at community gastroenterology clinics for non-liver-related reasons, HCV proportion was 1.7% for non-Asians and 2.9% for Asians. Screening for HCV should be offered to high-risk patients presenting to gastroenterology clinics with unrelated gastrointestinal complaints.


OBJECTIVE: The aim of this study was to explore the feasibility and the efficacy of a physiotherapy-led exercise program in changing the health status of a sample of patients with chronic hepatitis C. DESIGN: A single-blind randomized controlled trial was conducted in a sample of patients with iatrogenically acquired hepatitis C in Ireland. Twenty-two participants were recruited and randomly assigned to exercise (n = 10) and control (n = 12) groups. Both groups received a generic exercise advice leaflet, and the exercise group attended 12 exercise
sessions for 6 wks. A battery of physical performance measures and patient-reported outcome measures were assessed at baseline and 6 wks, with 1-yr follow-up of the self-reported measures. **RESULTS:** Significant group by time interactions during the 6-wk period were found for pain (F1,20 = 5.15, P = 0.034), grip strength (F1,20 = 5.94, P = 0.024), aerobic capacity (F1,20 = 5.73, P = 0.024), and depression (F1,20 = 6.16, P = 0.022), with the exercise group showing greater positive change. The exercise group also had superior gains in the 36-Item Short-Form Health Survey vitality and social function scores (P < 0.05). The short-term gains were not sustained at 1 yr. **CONCLUSIONS:** This pilot study shows the feasibility of exercise in hepatitis C management, improving physical fitness, psychologic function, and quality-of-life without worsening symptoms in the short term.

**BACKGROUND:** Faldaprevir (BI 201335) and BI 207127 are direct-acting antiviral agents under development for the treatment of chronic hepatitis C virus infection. This article describes the final results of the phase 1b SOUND-C1 study which evaluated the interferon-free oral combination of faldaprevir, BI 207127, and ribavirin in 32 treatment-naïve patients infected with hepatitis C virus genotype 1. **METHODS:** Patients were randomized to receive BI 207127 400 mg (n=15) or 600 mg (n=17) three times daily plus faldaprevir 120 mg once daily and weight-based ribavirin for 4 weeks. Interferon-free therapy was followed by response-guided faldaprevir plus pegylated interferon alfa-2a/ribavirin to week 24 or 48. **RESULTS:** At week 4, 73% (11/15) and 100% (17/17) of patients in the BI 207127 400 mg and 600 mg groups achieved hepatitis C virus (HCV) RNA <25 IU/mL, respectively. During interferon-free treatment, virological breakthrough was reported in one patient and re-increase of HCV RNA in one patient. Both patients were successfully treated with interferon-containing therapy. The rate of sustained virological response 24 weeks after completion of treatment was 73% (11/15) in the BI 207127 400 mg group and 94% (16/17) in the 600 mg group. During faldaprevir plus pegylated interferon alfa-2a/ribavirin treatment, the most common adverse events were pruritus (38% of patients), rash (31%), and asthenia (31%); these were severe in≈3% of patients. **CONCLUSIONS:** Potent antiviral activity and favourable safety of the treatment regimen were demonstrated. Furthermore, the results suggest that patients with breakthrough at week 4 may be rescued with an interferon-containing regimen.

**BACKGROUND:** Viral kinetics and host interleukin 28B (IL-28B) genotype determine treatment outcome in hepatitis C virus genotype 1 (HCV-1) infection. **OBJECTIVES:** We aimed to explore the interplay between interferon responsiveness at treatment week 4 and IL28B genotype in the achievement of a sustained virological response (SVR; undetectable HCV RNA 24-weeks after end-of-treatment). **STUDY DESIGNS:** Rs8099917 genotypes were determined in 528 HCV-1 patients with peginterferon/ribavirin. Interferon responsiveness were evaluated by the degree of week 4 viral reduction: <1 log(10) IU/mL, 1-2 logs(10) IU/mL, 2-3 logs(10)
IU/mL, 3-4 logs(10) IU/mL and ≥4 logs(10) IU/mL reduction and/or undetectable HCV RNA, respectively. RESULTS: The SVR rate was significantly higher in patients with great interferon responsiveness at week 4. A great interferon responsiveness was associated with younger age (P < 0.0001), lower body mass index (P = 0.0056), lower aspartate aminotransferase levels (P = 0.0009), higher hemoglobin concentration (P = 0.0033), higher platelet counts (P < 0.0001), male gender (P < 0.0001) and rs809997 TT-genotype (P < 0.0001). Comparing to non-TT genotype patients, TT genotype patients had a significantly higher SVR rate with moderate viral reduction (1-3 logs(10) IU/mL) at week 4 (58.9% vs. 18.2%, P < 0.001), and the SVR rate did not differ between TT/non-TT patients on the extreme ends (<1 or >3 log(10) IU/mL reduction) of week 4 interferon responsiveness. For non-TT genotype carriers who were with <3 logs(10) reduction, none (0/15) could have a complete early virological response and only 10.9% (7/64) of the patients had an SVR. CONCLUSIONS: More profound interferon responsiveness is mandatory for HCV-1 patients with unfavorable IL-28B genotype.


BACKGROUND AND AIM: Host interleukin-28B (IL-28B) genetic variants determine a sustained virological response (SVR) in hepatitis C virus genotype 1 (HCV-1) treatment-naïve patients. Its impact on treatment-experienced Asian patients with peginterferon/ribavirin in is to be elucidated. METHODS: IL-28B rs8099917 genotype was determined in 70 HCV-1 treatment-experienced patients retreated with 48-week peginterferon/ribavirin. RESULTS: The SVR rate was 60.0% and was significantly higher in previous relapsers than in non-responders (72.7% and 13.3%, P<0.001). Multivariate analysis revealed that the most important factor predictive of an SVR was previous relapse (Odds ratio [OR]/95% C.I.: 14.76/2.72-80.06, P=0.002), followed by the carriage of rs8099917 TT genotype (OR/ 95% C.I.: 7.67/1.27-46.49, P=0.03). Comparing to patients with TG/GG genotype, those with TT genotype had significantly higher rates of rapid virological response (29.3% vs. 0%, P=0.03), end-of-treatment virological response (86.2% vs. 50.0%, P=0.01), SVR (69.0% vs. 16.7%, P=0.002) and lower relapse rate (22.0 % vs. 66.7%, P=0.04). The SVR rate was similarly low between previous non-responders with different rs8099917 genotypes (12.5% vs. 14.3%, P=1). On the contrary, previous relapsers with rs8099917 genotype had a significantly higher SVR rate than those who carried rs8099917 TG/GG genotype (78.0 % vs. 20.0%, P=0.02). Stepwise logistic regression analysis revealed that the only factor predictive of an SVR in previous relapsers was the carriage of rs809997 TT genotype (OR/ 95% CI:18.50/1.82-188.39, P=0.014). CONCLUSIONS: Host IL-28B genetic variants played a role in Asian relapsers but not non-responders retreated with peginterferon/ribavirin. Direct antiviral agents might be possibly avoidable in Asian relapsers with favorable IL-28B genotype.


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NK cells were found to play an important role in liver fibrosis, a process commonly seen in a chronic liver disease such as chronic hepatitis C (CHC). The aim of this study was to evaluate potential differences in relation to coexisting liver steatosis in children with chronic hepatitis C. The study group consisted of 31 children with chronic hepatitis, aged 7-18 years (mean = 15 ± 2 years). Blood samples were taken prior to liver biopsy. The METAVIR scale was used for histological evaluation. Peripheral lymphocytes were subjected to monoclonal antibodies to CD56 antigen, KIRs and NKG2D antigens. Cells were assayed by flow cytometry for the ratio of positive cells and mean fluorescence intensity (MFI). Results were evaluated regarding the presence of liver steatosis. Significantly higher mean AST activity as well as higher AST-to-platelets ratio index (APRI) was observed in a group of children with coexisting liver steatosis. These children had significantly higher MFI for CD158e and lower MFI for NKG2D. All CHC patients had significantly higher MFI for NKG2D than the controls. The proportion of cells with expression of CD158i, KIR2D and APRI was found independent predictors of liver steatosis in univariate analysis and body mass index in logistic regression. The expression of NK cell receptors is altered in coexisting steatosis that may influence long-term prognosis in CHC.


BACKGROUND: Cytokines and serotonin neurotransmission may play an important role on the development of psychopathological symptoms during interferon (IFN) treatment. The aim of the present study was to investigate the association between IFN-induced depression, anxiety and fatigue and functional genetic variants at the interleukin-6 gene (IL-6) and serotonin transporter gene (SERT). METHODS: 385 consecutive Caucasian outpatients with chronic hepatitis C initiating treatment with IFN-alpha and ribavirin were included. All patients were interviewed at baseline using the Structured Clinical Interview for DSM-IV (SCID-I) and those with a current major depressive disorder or anxiety disorder before starting treatment were excluded. Depression and anxiety were assessed at baseline during the treatment (at 4, 12, 24 and 48 weeks) using the Hospital Anxiety and Depression Scale and fatigue was evaluated using a visual analogue scale. The 5-HTTLPR region of SERT gene and the functional polymorphism located at the promoter region of IL-6 gene (rs1800795) were genotyped. RESULTS: Genotypic distribution was in the Hardy-Weinberg equilibrium for SERT (p=0.41) and for IL-6 (p=0.72) polymorphisms. At baseline we found only a significant effect of IL-6 polymorphism on fatigue symptoms. During antiviral treatment we reported that subjects with CC genotype (IL-6) presented significantly lower changes from baseline in IFN-induced depression (p=0.005) and IFN-induced anxiety (p=0.004). We did not find statistically significant differences on depression (p=0.21) or anxiety (p=0.15) between SS/SL and LL genotypes of SERT. CONCLUSIONS: Genetic variations in the IL-6 gene increase the risk of IFN-induced depression and anxiety. The IL-6 polymorphism was associated with fatigue rates in patients with chronic hepatitis C before treatment. Our study confirms the role of inflammatory mechanisms in IFN-induced psychopathological symptoms.

OBJECTIVES: The relationship between hepatitis C virus (HCV) infection and type 2 diabetes mellitus (DM 2) is still uncertain. The objective of this study was to evaluate the association between HCV infection, measured as positivity to anti-HCV antibodies, and the incidence of DM 2 in a cohort of subjects sampled from the general population and followed up for 20 years.

METHODS: At baseline, the cohort consisted of a random sample of 2,472 subjects (72% response rate, age range 30-69 years) from the electoral register of a town in Southern Italy. The cohort subjects were examined three times: in 1985 (M1), in 1992 (M2), and in 2005 (M3). At M1, M2, and M3, each participant filled in a questionnaire and had a blood sample taken to measure blood glucose and other serum variables including glutamic pyruvic alanine aminotransferase (ALT). Anti-HCV antibodies were analyzed with standard techniques at M1 and M2. Diabetes type 2 diagnosis was a history of diabetes and/or serum glucose ≥126 mg/dl and/or treatment with insulin or hypoglycemic drugs. Logistic regression was used for multivariable data analysis. RESULTS: Diabetes prevalence was higher in subjects with positive anti-HCV antibodies at M1 and M2, and diabetes incidence was higher in subjects with baseline positive anti-HCV antibodies at M1-M2 and lower at M2-M3. In multivariable models, controlling for gender, age, and body mass index (BMI), there was no association between incident cases of diabetes and positive anti-HCV antibodies at baseline, either at M1-M2 (odds ratio (OR) 0.73, 95% confidence interval (CI) 0.43-1.22) or at M2-M3 (0.65, 0.41-1.04). HCV was associated with DM 2 only in subjects with elevated ALT (OR 0.58, 95% CI 0.31-1.08, if ALT normal; OR 1.47, 95% CI 1-2.16, if ALT elevated, controlling for age, gender, and BMI).

CONCLUSIONS: Our findings, in a cohort study at population level, support an association between the presence of anti-HCV antibodies at baseline and a higher incidence of type 2 diabetes in the following 20 years only in subjects with elevated ALT.

Hepatitis C virus transmission during colonoscopy evidenced by phylogenetic analysis.

BACKGROUND: Nosocomial transmission events still play an important role in hepatitis C virus (HCV) spreading. Among most reported medical procedures involved in nosocomial transmission, endoscopy procedures remain controversial and might be underestimated.

OBJECTIVE: The aim of the study was to investigate a case of nosocomial person-to-person transmission of HCV in an endoscopy unit. STUDY DESIGN: An acute HCV infection was detected in a person that had undergone a colonoscopy after an HCV-infected patient. Serum samples from both persons were subjected to a molecular epidemiology study. The HCV NS5B genetic region was amplified and directly sequenced and the E1-E2 region was amplified, cloned and sequenced (20 clones per specimen). All sequences were subjected to phylogenetic analyses. A conventional epidemiological investigation was performed to determine the most likely cause of HCV transmission. RESULTS: NS5B sequence analysis revealed that both persons were infected with closely related HCV-1b strains. Furthermore, phylogenetic analysis of E1-E2 sequences evidenced a direct transmission between patients. The epidemiological investigation pointed out to anesthetic procedures as the most likely source of HCV transmission. The index case, not having spontaneously cleared the infection 10 months after infection, required antiviral treatment, which resulted in a sustained virological response. CONCLUSIONS: The molecular epidemiology study performed provided evidence of a person-to-person transmission of HCV.
during a colonoscopy procedure, and the anesthetic procedure was the most likely source of HCV transmission. This study highlights the importance of strictly following standard precautions by healthcare workers in order to prevent nosocomial HCV transmission.

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


Hepatitis C virus (HCV) is mainly hepatotropic; however, several reports document the presence of genomic viral RNA in extrahepatic sites including peripheral blood mononuclear cells (PBMCs). In this study, the presence of HCV RNA was initially evaluated in the plasma and peripheral blood mononuclear cells (PBMCs) of 53 HCV-infected patients who were treated per protocol. PBMC-associated HCV RNA was detectable in 79% of patients. Early virological response to combined pegylated interferon-α (PegIFN) and ribavirin (RBV) therapy in patients with undetectable levels of PBMCs-associated HCV RNA was 100%, while it was 60% (P = 0.003) in those who had detectable levels of PBMC-associated HCV RNA. A sustained virological response was observed in 35% of patients with detectable PBMC-associated HCV RNA, but was 70% in patients with undetectable levels of PBMC-associated HCV RNA (P = 0.07). In a multivariate analysis incorporating parameters such as HCV genotype, viral load, presence of cirrhosis and absence of PBMC-associated HCV RNA, a significant relationship was observed between the detection of PBMC-associated HCV RNA and the sustained virological response (OR 19.4, 95% CI: 2.1-486.2, P = 0.0061). The association between single nucleotide polymorphism (SNP) in IL28B, known predictor of antiviral therapy outcome, and the occurrence of HCV RNA in PBMC in 84 chronically infected patients was then evaluated. Results suggest that the presence of a G allele in rs8099917, known to associate to a poor response to PegIFN/RBV therapy, also predicts an increased association of HCV RNA with PBMC (OR: 3.564; 95% CI: 1.114-11.40, P = 0.0437).

**Genome-wide analysis of host mRNA translation during hepatitis C virus infection.**


In the model of Huh7.5.1 hepatocyte cells infected by the JFH1 hepatitis C (HCV) strain, transcriptomic and proteomic studies have evidenced modulations of pathways governing mainly apoptosis and cell cycling. Differences between transcriptomic and proteomic studies pointed out to regulations occurring at the post-transcriptional level including the control of mRNA translation. Here, we investigated at the genome-wide level, the translational regulation occurring during HCV infection. Sucrose gradient ultracentrifugation followed by microarray analysis was used to identify translationally-regulated mRNAs (mRNAs associated with ribosomes) from JFH1-infected and uninfected Huh-7.5.1 cells. Translationally regulated mRNAs were found to correspond to genes enriched in specific pathways including vesicular transport and post-transcriptional regulation. Interestingly, the strongest translational regulation was found for mRNAs encoding proteins involved in pre-mRNA splicing, mRNA translation, and protein folding. Strikingly, these pathways were not previously identified, through transcriptomic studies, as being modulated following HCV infection. Importantly, the observed
changes in host mRNA translation were directly due to HCV replication rather than to HCV entry since they were not observed in JFH1-infected Huh-7.5.1 cells treated with a potent HCV NS3 protease inhibitor. Overall this study highlights the need to consider, beyond transcriptomic or proteomic studies, the modulation of host mRNA translation as an important aspect of HCV infection.


BACKGROUND: Pathogens that establish chronic infection elicit immune responses with suppressive cytokines dominating over pro-inflammatory cytokines. Chronic hepatitis C virus (HCV) infection, human immunodeficiency virus (HIV) infection and simian immunodeficiency virus (SIV) infection are associated with high levels of antiviral antibodies expressing a common idioype specifically recognized by the 1F7 monoclonal antibody (mAb). The 1F7 mAb is a murine IgMκ antibody raised against immunoglobulin pooled from the plasma of multiple HIV-infected individuals. In this study, we investigated direct effects of the 1F7 mAb itself on peripheral blood mononuclear cells (PBMC). METHODS: Isolated monocytes or PBMC from healthy controls were incubated with the 1F7 mAb or IgMκ mAb control. Cytokine production was measured in cell culture supernatants by ELISA and cells producing interleukin-10 (IL-10) were identified by subset depletion and intracellular flow cytometry. Endotoxin tolerance was assessed by exposing monocytes to lipopolysaccharide (LPS) following 1F7 mAb or IgMκ mAb control pre-treatment and comparing tumor necrosis factor (TNF)-α levels in cell culture supernatants. RESULTS: The 1F7 mAb stimulated monocytes and CD36+ lymphocytes to produce IL-10 in a time and dose-dependent manner. Treatment of monocytes with 1F7 mAb also reduced their subsequent responsiveness to LPS stimulation. CONCLUSIONS: Induction of antibodies expressing the 1F7 idioype by chronic pathogens may facilitate IL-10 production and progression to chronic infection. Direct effects of IL-10 from human monocytes stimulated by 1F7-like antibodies, followed by monocyte transition to an alternatively activated phenotype illustrated by endotoxin tolerance, are two complementary features favouring a tolerogenic or non-responsive immunological environment.


BACKGROUND: Hepatitis C virus (HCV) infects approximately 3% of the world population and is the leading cause of liver disease, impacting hepatocyte metabolism, depending on virus genotype. Hepatic metabolic functions show rhythmic fluctuations with 24-h periodicity (circadian), driven by molecular clockworks ticking through translational-transcriptional feedback loops, operated by a set of genes, called clock genes, encoding circadian proteins. Disruption of biologic clocks is implicated in a variety of disorders including fatty liver disease, obesity and diabetes. The relation between HCV replication and the circadian clock is unknown. METHODS: We investigated the relationship between HCV core infection and viral replication and the expression of clock genes (Rev-Erbα, Rorα, ARNTL, ARNTL2, CLOCK, PER1, PER2, PER3, CRY1 and CRY2) in two cellular models, the Huh-7 cells transiently expressing the HCV
core protein genotypes 1b or 3a, and the OR6 cells stably harboring the full-length hepatitis C genotype 1b replicon, and in human liver biopsies, using qRT-PCR, immunoblotting, luciferase assays and immunohistochemistry. **RESULTS:** In Huh-7 cells expressing the HCV core protein genotype 1b, but not 3a, and in OR6 cells, transcript and protein levels of PER2 and CRY2 were downregulated. Overexpression of PER2 led to a consistent decrease in HCV RNA replicating levels and restoration of altered expression pattern of a subset of interferon stimulated genes (ISGs) in OR6 cells. Furthermore, in liver biopsies from HCV genotype 1b infected patients, PER2 was markedly localized to the nucleus, consistent with an auto-inhibitory transcriptional feedback loop. **CONCLUSIONS:** HCV can modulate hepatic clock gene machinery, and the circadian protein PER2 counteracts viral replication. Further understanding of circadian regulation of HCV replication and rhythmic patterns of host-hosted relationship may improve the effectiveness of HCV antiviral therapy. This would extend to hepatic viral infections the current spectrum of chronotherapies, implemented to treat metabolic, immune related and neoplastic disease.


We examined the association of TIMP-1 and TIMP-2 gene polymorphisms with the progression of chronic liver disease related to the hepatitis C virus (HCV). We used PCR to analyze 188 patients with HCV-related liver disease (95 with chronic hepatitis and 93 with cirrhosis) for TIMP-1 372 T/C and TIMP-2 -418 G/C polymorphisms. Comparing chronic hepatitis and cirrhosis, there were no significant differences in TIMP-1 and TIMP-2 gene polymorphisms. Among chronic hepatitis patients, TIMP-2 -418 G homozygotes showed significantly faster fibrosis progression than C carriers. Among cirrhotic patients, males with the TIMP-1 372 T allele developed cirrhosis at a younger age, and patients who were homozygous for the higher-transcription TIMP-2 -418 G allele had significantly lower serum albumin concentrations. These results suggest that faster progression of liver fibrosis could be associated with TIMP-2 -418 G homozygotes.


Coumarins and coumestans represent an important family of compounds with diverse pharmacological properties. We recently identified coumestans as novel inhibitors of hepatitis C virus NS5B polymerase and predicted their binding in thumb pocket-1 (TP-1) of NS5B. As the coumarins are structurally related to coumestans by virtue of their common A- and B-rings, we postulated them to also exhibit similar binding interaction with NS5B and inhibit its polymerase function. We therefore investigated 24 coumarin and neoflavone derivatives as candidate NS5B inhibitors and identified 14 compounds inhibiting NS5B polymerase activity with IC50 values between 17 and 63 μm. Of these, the newly synthesized 6,8-diallyl-5,7-dihydroxycoumarin (8a) was produced in three steps in high chemical yield from floroglucinol and found to be the most potent of this series, exhibiting activity similar to the reference coumestan LQB-34. The binding site of 8a was mapped to TP-1 of NS5B by counter screening against P495L NS5B mutant.

Increased $\gamma$-glutamyl transferase (GGT) activity is associated with liver injury and with mortality in the general population. Less is known about its association with chronic hepatitis C (HCV) outcomes. We examined GGT as a predictor of both virological response to treatment and long-term clinical outcomes in the Hepatitis C Anti-viral Treatment Against Cirrhosis Trial (HALT-C). HALT-C enrolled patients with advanced liver disease (Ishak fibrosis score $\geq$3) in two phases: a lead-in to establish lack of sustained viral response with full dose pegylated interferon (IFN) and ribavirin followed by a 3.5-year randomized trial with low-dose IFN. Low-dose IFN did not prevent liver disease progression, and patients were then followed for up to an additional 5 years off therapy. Analyses were performed for 1,319 patients who had GGT measured prior to initiation of treatment. Increases in risk with each increase in quintile of GGT (10-57, 58-89, 90-139, 140-230, 231-2,000 IU/L) were determined by logistic regression for treatment response or Cox regression for clinical outcomes. Baseline GGT was associated with male sex, nonwhite ethnicity, diabetes and insulin resistance, interleukin (IL)28B rs12979860 CT and TT genotypes, and numerous markers of liver disease injury and severity. In the lead-in phase, increasing GGT was strongly associated with diminished week 20 response, end of treatment response, and sustained virological response in both univariate and multivariate analyses controlling for factors known to be associated with treatment response (P < 0.0001). GGT was also associated with all clinical outcomes in univariate and multivariate analysis (P < 0.05) except for hepatocellular carcinoma (P = 0.46 in multivariate analysis). Conclusion: GGT is an independent predictor of both virological response and clinical outcomes among patients with advanced liver disease due to HCV.

Hepatitis C Virus Core Protein Down-Regulates p21(Waf1/Cip1) and Inhibits Curcumin-Induced Apoptosis through MicroRNA-345 Targeting in Human Hepatoma Cells.

BACKGROUND: Hepatitis C virus (HCV) has been reported to regulate cellular microRNAs. The HCV core protein is considered to be a potential oncoprotein in HCV-related hepatocellular carcinoma, but HCV core-modulated cellular microRNAs are unknown. The HCV core protein regulates p21(Waf1/Cip1) expression. However, the mechanism of HCV core-associated p21(Waf1/Cip1) regulation remains to be further clarified. Therefore, we attempted to determine whether HCV core-modulated cellular microRNAs play an important role in regulating p21(Waf1/Cip1) expression in human hepatoma cells. METHODS: Cellular microRNA profiling was investigated in core-overexpressing hepatoma cells using TaqMan low density array. Array data were further confirmed by TaqMan real-time qPCR for single microRNA in core-overexpressing and full-length HCV replicon-expressing cells. The target gene of microRNA was examined by reporter assay. The gene expression was determined by real-time qPCR and Western blotting. Apoptosis was examined by annexin V-FITC apoptosis assay. Cell
cycle analysis was performed by propidium iodide staining. Cell proliferation was analyzed by MTT assay. **RESULTS:** HCV core protein up- or down-regulated some cellular microRNAs in Huh7 cells. HCV core-induced microRNA-345 suppressed p21(Waf1/Cip1) gene expression through targeting its 3’ untranslated region in human hepatoma cells. Moreover, the core protein inhibited curcumin-induced apoptosis through p21(Waf1/Cip1)-targeting microRNA-345 in Huh7 cells. **CONCLUSION AND SIGNIFICANCE:** HCV core protein enhances the expression of microRNA-345 which then down-regulates p21(Waf1/Cip1) gene expression. It is the first time that HCV core protein has ever been shown to suppress p21(Waf1/Cip1) gene expression through miR-345 targeting.


Successful viral infection requires intimate communication between virus and host cell, a process that absolutely requires various host proteins. However, current efforts to discover novel host proteins as therapeutic targets for viral infection are difficult. Here, we developed an integrative-genomics approach to predict human genes involved in the early steps of hepatitis C virus (HCV) infection. By integrating HCV and human protein associations, co-expression data, and tight junction-tetraspanin web specific networks, we identified host proteins required for the early steps in HCV infection. Moreover, we validated the roles of newly identified proteins in HCV infection by knocking down their expression using small interfering RNAs. Specifically, a novel host factor CD63 was shown to directly interact with HCV E2 protein. We further demonstrated that an antibody against CD63 blocked HCV infection, indicating that CD63 may serve as a new therapeutic target for HCV-related diseases. The candidate gene list provides a source for identification of new therapeutic targets.

**HIV/HCV COINFECTION**


**BACKGROUND:** It is unclear whether PEG-IFN-induced severe neutropenia in HIV-HCV coinfected subjects is associated to increased risk of serious infections. **METHODS:** Prospective cohort study between 2000-2012 in HIV-HCV coinfected subjects initiating treatment with PEG-IFN+RBV. Infections were defined as serious when patients required hospitalization, treatment discontinuation, or the patient died. Potential risk factors for infection and the association between neutropenia (severe, <500 cells/μL and non severe, 500-1500 cells/μL) and infections (serious infections and infections of any severity) were determined by logistic regression analysis. **RESULTS:** From 418 subjects (3928 person-weeks of therapy), infections occurred in 123 (29%) subjects, accounting for 149 episodes (3.8 infections per 100 person-weeks of therapy). Most infections (47%) involved the upper respiratory tract and were minor. After a multivariate analysis adjusting by age, sex, CD4 count, AIDS, antiretroviral therapy, cirrhosis, neutrophil count, type of PEG-IFN and G-CSF use, none of these variables remained independently associated with the risk of infection. Twenty subjects developed a serious
infection (5% of all the patients), accounting for 0.5 episodes per 100 person-weeks of therapy. The frequency of serious infections was higher in subjects with severe neutropenia compared to those with non-severe neutropenia and without neutropenia, although no statistically significant (8.6%, 4.8%, 3.6%, respectively; trend test P=0.281). After multivariate analyses, neutropenia was not independently associated to increased risk of serious infections. **CONCLUSIONS:** In this large prospective cohort of HIV-infected patients treated with PEG-IFN+RBV for chronic C hepatitis, serious infections were uncommon, non-fatal and unrelated to PEG-IFN induced severe neutropenia.

**OBJECTIVE:** To determine hepatitis C virus (HCV) RNA clearance from blood and saliva of HIV-HCV-coinfected patients undergoing combined therapy with pegylated interferon plus ribavirin (PEG-IFN-RIB). **SUBJECTS AND METHODS:** Study group was formed of 60 HIV-infected patients with chronic hepatitis C who were starting treatment with PEG-IFN-RIB. Blood and saliva samples were taken at baseline, at the end of treatment and 24 and 48 weeks later. A nested RT-PCR technique was used to detect HCV-RNA in saliva. **RESULTS:** HCV-RNA was detected in saliva at baseline in 64.7% of patients. Thirty-four patients completed follow-up. The response rate (undetectable HCV-RNA) in blood was 79.4% at the end of treatment; 55.8% at 24 weeks after the end of treatment and 50% at 48 weeks. HCV was detected in saliva of 13 (38.2%) patients at the end of treatment and in 18 (52.9%) patients at 24 and 48 weeks later. Concordance of HCV clearance from blood and saliva reached its maximum value at 48 weeks after the end of treatment (odds ratio, 112.51). **CONCLUSION:** In HIV-HCV-coinfected patients responders to PEG-IFN-RIB, the salivary glands do not appear to be a sanctuary site for HCV, although viral clearance from saliva may be slower than from blood.

**BACKGROUND AND AIMS:** The influence of HCV-RNA levels and genotype on HCV disease progression is not well studied. The prognostic value of these markers was investigated in HIV/HCV co-infected individuals from the EuroSIDA cohort. **METHODS:** EuroSIDA is a prospective cohort of 18295 HIV-1 infected patients in 105 centres across Europe, Israel and Argentina. All subjects with known HCV antibody (HCVAb) status (n=13025) were enrolled in the present study. **RESULTS:** 4044 (31.0%) patients had detectable HCVAb. After adjustment, HCVAb+ patients had an increased incidence of liver-related death (LRD) compared to HCVAb-individuals (IRR 8.90; 95% CI 5.60 - 14.14, p<0.0001). Information on HCV-RNA was available for 2709 (67.0%) HCVAb+ patients and 2010 (74.2%) were HCV-RNA+. Of 1907 patients with HCV genotype measured, 1008 (52.9%), 62 (3.3%), 567 (29.7%) and 270 (14.2%) were infected with genotype 1, 2, 3 and 4, respectively. Patients with detectable HCV-RNA had similar incidence of non-LRD, but higher incidence of LRD compared to HCVAb+ aviremic patients (adjusted IRR 1.18; 95% CI 0.93 - 1.50, p=0.17) and (adjusted IRR 2.11; 95% CI 1.30 - 3.42, p=0.0025), respectively. In patients with HCV viremia, HCV-RNA levels and HCV
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genotype did not influence the risk of non-LRD or LRD. CONCLUSIONS: HCV seropositive HIV patients had a 9-fold increased risk of LRD compared to patients who were HCV seronegative. Risk of death from any cause or LRD was not influenced by level of HCV viremia or HCV genotype.


Previous reports have suggested a poor renal prognosis in patients with HIV and HCV co-infection with a preponderance of immune complex mediated glomerular disease on biopsy. Although the benefits of HAART on HIVAN are known, its impact on co-infected patients is unclear. We describe the renal biopsy findings and renal outcome in 29 co-infected patients in the HAART era and compare them to findings in 14 historical controls reported from our institution in the pre-HAART era. Our present cohort was predominantly male and Black with the majority reporting a history of intravenous (i.v.) drug use. Renal biopsy findings included 16 patients with immune complex mediated glomerular disease and 14 patients with FSGS, of which only 3 had collapsing features and/or tubular microcysts typical of HIVAN. Five patients had other biopsy diagnoses not directly related to viral infection. Median renal survival in our cohort was 15.6 months - significantly better than the 1.7 months seen our pre-HAART cohort. The modern cohort's improved renal outcome occurred despite older patients, longer HIV infection and similar levels of renal insufficiency. Our data indicate a changing epidemiology and natural history of renal disease in the HAART era with less immune complex mediated glomerular disease and more non-collapsing FSGS of the usual type. The marked improvement is likely to be multifactorial, including use of antiretroviral and anti-HCV therapies, RAAS antagonists, earlier nephrology referral and generally improved medical care.

Epidemiology, Diagnostics, and Miscellaneous Works


Those working in the fields of harm reduction, healthcare, and human services must cope with a range of stresses, including post traumatic stress and vicarious trauma. Pain and loss are just a part of the job. So is dealing with premature death as a result of HIV, hypertension, and even overdose. Faced with a range of challenges, some workers in the field even turn to self-medication. For some, it is about pleasure; for others it is about alleviating suffering. In recent years, several leaders in the AIDS and harm reduction fields have died ahead of their time. Some stopped taking their medications; others overdosed. Rather than weakness or pathology, French sociologist Emile Durkheim saw self-destructive behavior as a byproduct of social disorganization and isolation, as a way of contending with a breakdown of social bonds and alienation. There are any number of reasons why such behavior becomes part of work for those involved with battling the dueling epidemics of Hepatitis C, HIV, and related concerns. Forms of stress related to this work include secondary trauma, compassion fatigue, organizational conflict, burnout, complications of direct services, and lack of funding. Faced with day-to-day struggles over poverty, punitive welfare systems, drug use, the war on drugs, high risk behavior, structural
violence, and illness, many in the field are left to wonder how to strive for wellness when taking on so much pain. For some, self-injury and self-medication are ways of responding. Building on ethnographic methods, this reflective analysis considers the stories of those who have suffered, as well as a few of the ways those in the field cope with harm and pain. The work considers the moral questions we face when we see our friends and colleagues suffer. It asks how we as practitioners strive to create a culture of wellness and support in the fields of harm reduction, healthcare, and human services. Through a brief review of losses and literature thereof, the essay considers models of harm reduction practice that emphasize health, pleasure and sustainability for practitioners.

**A global view of hepatitis C: Physician knowledge, opinions, and perceived barriers to care.**


Chronic infection with the hepatitis C virus (HCV) is a leading cause of global morbidity and mortality. Although recent advances in antiviral therapy have led to significant improvements in treatment response rates, only a minority of infected patients are treated. Multiple barriers may impede the delivery of HCV therapy. The aim of this study was to identify perceived barriers to care, knowledge, and opinions among a global sample of HCV treatment providers. An international, multidisciplinary survey of HCV treatment providers was conducted. Each physician responded to a series of 214 questions concerning his or her practice characteristics, opinions regarding the state of HCV care, knowledge regarding HCV treatment, and perception of treatment barriers. A total of 697 physicians from 29 countries completed the survey. Overall, physicians viewed patient-level barriers as most significant, including fear of side effects and concerns regarding treatment duration and cost. There were distinct regional variations, with Central and Eastern European physicians citing government barriers as most important. In Latin America, the Middle East, and Africa, payer-level barriers, including lack of treatment coverage, were prominent. Overall, the perception of barriers was strongly associated with physician knowledge, experience, and region of origin, with the fewest barriers reported by Nordic physicians and the most reported by Middle Eastern and African physicians. Globally, physicians demonstrated deficits in basic treatment principles, including the role of viral kinetics and the management of treatment nonresponders. Two thirds of surveyed physicians believed that patients do not have adequate access to providers in their community. **CONCLUSION:** Barriers to HCV treatment vary globally, though patient-level factors are viewed as most significant by treating physicians. Efforts to improve awareness, education, and specialist availability are needed.

**The Association Between Law Enforcement Encounters and Syringe Sharing Among IDUs on Skid Row: A Mixed Methods Analysis.**

Wagner KD, Simon-Freeman R, Bluthenthal RN. AIDS Behav. 2013 Apr 26. [Epub ahead of print]
The legal environment is one factor that influences injection drug users' (IDUs) risk for HIV and other bloodborne pathogens such as hepatitis C virus (HCV). We examined the association between law enforcement encounters (i.e., arrests and citations) and receptive syringe sharing among IDUs in the context of an intensified policing effort. We conducted a mixed methods analysis of 30 qualitative and 187 quantitative interviews with IDUs accessing services at a Los Angeles, CA syringe exchange program from 2008 to 2009. Qualitative findings illustrate concerns related to visibility, drug withdrawal, and previous history of arrest/incarceration. In quantitative analysis, the number of citations received, current homelessness, and perceiving that being arrested would be a "big problem" were independently associated with recent syringe sharing. Findings illustrate some of the unintended public health consequences associated with intensified street-level policing, including risk for HIV and HCV transmission.


BACKGROUND: Liver stiffness and non-invasive tests predict overall survival in chronic hepatitis C. However, in patients chronically infected with hepatitis B virus (HBV), only the association between liver stiffness and the risk of hepatocellular carcinoma has been published.

AIM: To evaluate the 5-year prognostic value of liver stiffness, non-invasive tests of liver fibrosis, and liver biopsy, to predict overall survival in chronic hepatitis B.

METHODS: In a consecutive cohort, we prospectively assessed fibrosis, with liver stiffness, FibroTest, APRI, FIB-4 and liver biopsy (if indicated). We examined death and liver transplantation during a 5-year follow-up, and factors associated with overall survival.

RESULTS: A total of 600 patients (men 64%, mean age 42 years, inactive carriers 36%) with chronic hepatitis B were included. At 5 years, 25 patients were dead (13 liver-related deaths) and four patients had liver transplantation. Overall survival was 94.1% and survival without liver-related death 96.3%. No liver-related death was observed in inactive carriers. Survival was significantly decreased in patients diagnosed with severe fibrosis, whatever the non-invasive method used (P < 0.0001), or liver biopsy (P = 0.02). Patients' prognosis decreased as liver stiffness and FibroTest increased. In multivariate analysis, FibroTest and liver stiffness had the highest hazard ratio with survival. The association persisted after adjustment on age, necro-inflammatory histological activity presumed by ActiTest and treatment.

CONCLUSIONS: Liver stiffness measurement or FibroTest can predict survival in chronic HBV infection. Thus, these tools may help physicians to early assess prognosis and discuss specific treatments, such as liver transplantation.

Telaprevir: Clinical Pharmacokinetics, Pharmacodynamics, and Drug-Drug Interactions.

This article provides an unbiased review of the pharmacokinetic, pharmacodynamic, and drug-drug interaction data of telaprevir, an NS3/4A protease inhibitor. Telaprevir is well absorbed with fatty food, moderately protein bound (59-76 %) with a large volume of distribution (~252 L), primarily metabolized by cytochrome P450 (CYP) 3A4 and P-glycoprotein, and is largely excreted into feces. Pharmacokinetic and pharmacodynamic parameters are well described in healthy subjects and individuals infected with hepatitis C virus (HCV), although only limited
data are available in specific patient subpopulations. Telaprevir is recommended to be given at 750 mg by mouth every 8 h for 12 weeks, in combination with peginterferon and ribavirin (the standard care). The addition of telaprevir to the standard care regimen results in increased sustained virological response in treatment-naive patients (30 %) and treatment-experienced patients (up to 50 %), and works synergistically to lower viral resistance. Telaprevir is a substrate and/or inhibitor of CYP3A4 and P-glycoprotein, and drug-drug interaction studies in humans have focused on these pathways. Based on our analysis, a few reported drug-drug interactions may be classified as clinically significant, but more experiments under dosing conditions that resemble those given in the clinic are needed to understand the relevance of some of the reported interactions. Future studies should focus on the pharmacokinetics/pharmacodynamics of telaprevir in special populations or patients with concomitant conditions that will likely co-exist with HCV infection, with an emphasis on establishing pharmacokinetic-pharmacodynamic relationships. In vitro characterization of other phase 1-3 metabolic pathways could assist in elucidating the mechanisms of the drug-drug interactions observed in humans.


Gender-specific medicine is the study of how diseases differ between men and women in terms of prevention, clinical signs, therapeutic approach, prognosis, psychological and social impact. It is a neglected dimension of medicine. In this review we like to point out some major issues in five enormous fields of medicine: cardiovascular diseases (CVDs), pharmacology, oncology, liver diseases and osteoporosis. CVDs have been studied in the last decades mainly in men, but they are the first cause of mortality and disability in women. Risk factors for CVD have different impacts in men and women; clinical manifestations of CVD and the influence of drugs on CVD have lot of gender differences. Sex-related differences in pharmacokinetics and pharmacodynamics are also emerging. These differences have obvious relevance to the efficacy and side effect profiles of various medications in the two sexes. This evidence should be considered for drug development as well as before starting any therapy. Gender disparity in cancer incidence, aggressiveness and prognosis has been observed for a variety of cancers and, even if partially known, is underestimated in clinical practice for the treatment of the major types of cancer. It is necessary to systematize and encode all the known data for each type of tumor on gender differences, to identify where this variable has to be considered for the purposes of the prognosis, the choice of treatment and possible toxicity. Clinical data suggest that men and women exhibit differences regarding the epidemiology and the progression of certain liver diseases, i.e., autoimmune conditions, genetic hemochromatosis, non-alcoholic steatohepatitis and chronic hepatitis C. Numerous hypotheses have been formulated to justify this sex imbalance including sex hormones, reproductive and genetic factors. Nevertheless, none of these hypothesis has thus far gathered enough convincing evidence and in most cases the evidence is conflicting. Osteoporosis is an important public health problem both in women and men. On the whole, far more epidemiologic, diagnostic and therapeutic studies have been carried out in women than in men. In clinical practice, if this disease remains underestimated in women, patients' and physicians' awareness is even lower for male osteoporosis, for which diagnostic and therapeutic strategies are at present less defined. In conclusion this review emphasizes the urgency of basic science and clinical research to increase our understanding of the gender differences of diseases.

Therapy for hepatitis C virus (HCV) is a rapidly evolving field wherein traditional treatment with the nonspecific antiviral agents pegylated interferon (IFN)-alpha and ribavirin has been and will continue to be supplanted by combinations of targeted therapies against HCV with and without concomitant pegylated IFN and/or ribavirin, resulting in markedly superior rates of viral clearance. Exhaustive study of HCV structure and replication through the development of in vitro systems have enabled the development of numerous novel direct acting antiviral agents that currently are undergoing clinical trials. As our understanding of the HCV virus and its antiviral targets increases, the future of HCV therapy holds the promise of high rates of viral eradication in all patient populations, many or all of whom will be treatable with IFN-free combinations of all-oral agents.

Liver Cancer


Novel therapeutic strategies are needed to treat patients with advanced hepatocellular carcinoma (HCC). Combination therapy of sorafenib and type I interferon (IFN) has substantial activity in patients with metastatic renal cell carcinoma. We investigated the antiproliferative effects of sorafenib in combination with pegylated interferon-α2b (PEG-IFN-α2b) on human hepatocellular carcinoma (HCC) cells in vitro and in vivo. A poorly differentiated HCC cell line derived from a patient with hepatitis C virus infection, HAK-1B and the moderately differentiated HCC cell line KIM-1 were used in this study. We demonstrated a synergistic antiproliferative effect of combination therapy on HAK-1B cells in vitro. In the in vivo study, a significant reduction of tumor volume and weight were observed in the combination group in both HAK-1B and KIM1 tumors, although synergistic effects were not clearly observed. The density of CD34 positive microvessels was significantly lower and cleaved caspase 3-positive apoptotic cell numbers were higher, in the sorafenib group and the combination group compared to the control or PEG-IFN-α2b group in both HAK-1B and KIM-1 tumors. Ki67 labeling index was significantly lower in the combination group compared to the control group in KIM-1 tumors. In conclusion, our results suggest that the combination therapy may be more effective for the treatment of HCC cases with variable sensitivity to antitumor effects of single therapy with either sorafenib or PEG-IFN-α2b.

Hepatocellular carcinoma (HCC) is the third leading cause of cancer death worldwide. Hepatocarcinogenesis is a multistep process mainly associated with persistent infection with hepatitis B (HBV) or C (HCV) viruses and always involving the accumulation of genetic alterations over decades of chronic liver disease. Mutations in TP53 and CTNNB1 genes are considered the cancer drivers for HCC development with variable frequencies depending on the etiology. Here we present a comprehensive review evaluating somatic mutations in TP53 and CTNNB1 genes in HBV- and HCV-related HCCs. Moreover, we report the mutational analysis of TP53 (exons 4-9) and CTNNB1 (exon 3) as well as PIK3CA (exon 9) in HCC from Southern Italy. The overall mutation frequency of TP53 and CTNNB1 was 33.3%, while hotspot variations in PIK3CA were completely absent. CTNNB1 mutations were significantly associated with young age (P=0.019) and moderately/poorly differentiated HCV-related HCC (P=0.015). The extended analysis of genetic alterations will help to identify molecular markers for liver cancer prevention, diagnosis and treatment of HBV and HCV-associated liver cancer.


The detection and diagnosis of hepatocellular carcinoma (HCC) at an early stage may significantly affect the prognosis of HCC patients. Thus, it is necessary to always identify novel putative markers for improving diagnosis. Hepatocarcinogenesis correlates with pathological hepatic angiogenesis. However, each tumor-induced angio-genetic process is influenced by the microenvironment through several pro- and anti-angiogenic factors released from tumor cells, tumor-associated inflammatory cells and/or from the extracellular matrix, and modulated by various signal pathways. In this study, we evaluated the profiling of angiogenic factors using Bio-Plex Pro™ Human Cancer Biomarker Panel 1, a 16-plex magnetic bead-based assay, in sera of patients with chronic hepatitis C (CHC) virus, liver cirrhosis (LC) and HCC. Our results demonstrated: i) high levels of hepatocyte growth factor (HGF) and prolactin only in LC and HCC patients, ii) high levels of soluble human epidermal growth factor receptor 2 (sHER-2/neu; ErbB-2), sIL-6Ra, leptin (LEP) and platelet endothelial cell adhesion molecule 1 (PECAM-1) in CHC, LC and HCC patients and iii) that sIL-6R correlated with the fibrosis stage in CHC patients, with Child Pugh score in those patients with LC and with tumor size in those patients with HCC, confirming that this protein may be used as a predictor of liver damage and of inflammatory process leading to fibrosis, cirrhosis, and subsequently to cancer. Moreover, an interactomic study conducted using the Ingenuity Pathway Analysis (IPA) software proved the existence of a correlation between 5 significant proteins [ErbB-2, sIL-6Ra, prolactin (PRL), HGF and LEP] which are involved in the same metabolic pathways.

Hepatitis C virus (HCV) infection is the major cause of hepatocellular carcinoma (HCC) in Japan. We previously identified the association of SNP rs2596542 in the 5' flanking region of the MHC class I polypeptide-related sequence A (MICA) gene with the risk of HCV-induced HCC. In the current study, we performed detailed functional analysis of 12 candidate SNPs in the promoter region and found that a SNP rs2596538 located at 2.8 kb upstream of the MICA gene affected the binding of a nuclear protein(s) to the genomic segment including this SNP. By electrophoretic mobility shift assay (EMSA) and chromatin immunoprecipitation (ChIP) assay, we identified that transcription factor Specificity Protein 1 (SP1) can bind to the protective G allele, but not to the risk A allele. In addition, reporter construct containing the G allele was found to exhibit higher transcriptional activity than that containing the A allele. Moreover, SNP rs2596538 showed stronger association with HCV-induced HCC (P=1.82×10^{-5} and OR=1.34) than the previously identified SNP rs2596542. We also found significantly higher serum level of soluble MICA (sMICA) in HCV-induced HCC patients carrying the G allele than those carrying the A allele (P=0.00616). **In summary**, we have identified a functional SNP that is associated with the expression of MICA and the risk for HCV-induced HCC.


The effects of interferon (IFN) treatment and the post-IFN treatment α-fetoprotein (AFP) levels on risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C (CHC) are unknown. To determine the relationship between AFP and alanine transaminase (ALT) levels and HCC risk, the cohort consisted of 1818 patients histologically proven to have CHC treated with IFN were studied. Cumulative incidence and HCC risk were analyzed over a mean follow-up period of 6.1 years using the Kaplan-Meier method and Cox proportional hazard analysis. HCC developed in 179 study subjects. According to multivariate analysis, older age, male gender, advanced fibrosis, severe steatosis, lower serum albumin levels, sustained virological response (SVR), and higher post-IFN treatment ALT or AFP levels were identified as independent factors significantly associated with HCC development. Cutoff values for ALT and AFP for prediction of future HCC were determined as 40 IU/L and 6.0 ng/mL, respectively, and negative predictive values of these cutoffs were high at 0.960 in each value. Cumulative incidence of HCC was significantly lower in patients whose post-IFN treatment ALT and AFP levels were suppressed to less than the cutoff values even in non-SVR patients. This suppressive effect was also found in patients whose post-IFN treatment ALT and AFP levels were reduced to less than the cutoff values despite abnormal pre-treatment levels. Conclusion: Post-IFN treatment ALT and AFP levels are significantly associated with the hepatocarcinogenesis. Measurement of these values is useful for predicting future HCC risk after IFN treatment. Suppression of these values after IFN therapy reduces HCC risk even in patients without HCV eradication.


Oral tegafur/uracil therapy has been indicated for patients with hepatocellular carcinoma (HCC) and is often used as a single-agent treatment. However, how the treatment efficacy is related to
5-fluorouracil (5-FU) metabolic enzymes is unclear. We investigated genetic polymorphisms of the 5-FU metabolic enzymes in Japanese patients with HCC. We examined two genetic polymorphisms of the metabolic enzymes cytochrome P450 2A6 (CYP2A6) and dihydropyrimidine dehydrogenase (DPD) in 58 Japanese hepatitis C virus-seropositive HCC patients. To measure efficacy, we investigated genetic polymorphisms of the variable number of tandem repeats (VNTRs) of thymidylate synthase (TS) and classified the genotypes as high or low expression types. The frequency of the CYP2A6*4 allele (no-activity allele) among 58 HCC patients was 0.233 and a homozygous genotype (*4/*4) was found in five patients. The heterozygous genotype (T/C) of DPYD*9 (T85C) was detected in eight patients and the frequency of the DPYD*9 allele among 58 HCC patients was 0.069. Of 58 patients, 42 were classified as high expression type and 16 as low expression type for TS VNTR. Fifteen of these 16 patients appeared to have normal CYP2A6 metabolic activity and 13 of these 15 patients likely had normal DPD metabolic activity. Only 13 of 58 HCC patients (22.4%) tested may respond positively to treatment with oral tegafur/uracil. Therefore, when administering oral 5-FU in patients with HCC, it is important to consider three genetic polymorphisms (CYP2A6, DPD, and TS) associated with 5-FU metabolic enzymes.


BACKGROUND: Metastatic tumor antigen 1 (MTA1) overexpression is closely associated with postoperative recurrence of hepatocellular carcinoma (HCC). It has been suggested that pegylated interferon (Peg-IFN) can prevent the occurrence of HCC in patients who have chronic viral hepatitis. In this study, the authors examined whether postoperative adjuvant Peg-IFN therapy can reduce the recurrence of MTA1-positive HCC after curative surgical resection.

METHODS: In this case-control study, 93 patients with MTA1-positive HCC who underwent curative surgical resection were prospectively enrolled. The median patient age was 53 years (range, 27-78); there were 65 men and 28 women; the etiology was hepatitis B virus (HBV) in 77 patients, hepatitis C virus (HCV) in 6 patients, and non-HBV/non-HCV in 10 patients; 31 patients received Peg-IFN (Peg-INTRON® ) subcutaneously at a dose of 50 μg per week for 12 months (the Peg-IFN group); and the remaining 62 patients were followed only and did not receive any adjuvant therapies (control group). Patients were followed every 1 to 3 months for a median of 24 months. RESULTS: HCC recurred postoperatively in 26 of 93 patients (28%), and 9 patients (10%) died during follow-up. The overall cumulative recurrence rates were significantly lower in the Peg-IFN group than in the control group (7% and 14% vs 24% and 34% at 1 year and 2 years, respectively; P < .05). In addition, the 1-year and 2-year cumulative survival rates were higher in the Peg-IFN group compared with the control group (100% vs 93% and 100% vs 87%, respectively; P < .05). In multivariate analysis, the receipt of adjuvant Peg-IFN therapy, in addition to having a lower Cancer of the Liver Italian Program score and being a woman, was an independent, favorable factor for a lower risk of postoperative recurrence.

CONCLUSIONS: The current data indicate that adjuvant Peg-IFN therapy may reduce the recurrence of HCC in patients who have MTA1-positive HCC after curative surgical resection.

BACKGROUND & AIMS: Due to the phenotypic and molecular diversity of hepatocellular carcinomas (HCC), it is a challenge to determine patients' prognosis. We aimed to identify new prognostic markers of patients with HCC treated by liver resection. METHODS: We collected 314 HCC samples from patients at Bordeaux (1998-2007) and Créteil (2003-2007) hospitals in France. We analyzed the gene expression patterns of the tumors and compared expression patterns with patient survival times. Using the coefficient and regression formula of the multivariate Cox model, we identified a '5-gene score' associated with survival times. This molecular score was then validated in 2 groups of patients from Europe, the United States (n=213), and China (n=221). RESULTS: The 5-gene score, based on combined expression level of HN1, RAN, RAMP3, KRT19, and TAF9, was associated with disease-specific survival times of 189 patients with resected HCC in Bordeaux (hazard ratio [HR], 3.5; 95% confidence interval [CI], 1.9-6.6; P<.0001). The association between the 5-gene score and disease-specific survival was validated in an independent cohort of 125 patients in Créteil (HR, 2.3; 95% CI, 1.1-4.9; P<.0001). The 5-gene score more accurately predicted patient outcomes than previously reported gene expression signatures. In multivariate analyses, the 5-gene score was associated with disease specific survival, independently of other clinical and pathology feature of HCC. Disease-specific survival was also predicted by combining data on microvascular invasion, the Barcelona Clinic Liver Cancer classification system, and the 5-gene score in a nomogram. The prognostic accuracy of the 5-gene score was further validated in European and US patients with hepatitis C, cirrhosis, and HCC (overall survival P=.002) and Asian patients with HCC with hepatitis B (overall survival, P=.02). Combining the 5-gene score with the expression pattern of 186 genes in corresponding cirrhotic tissues increased its prognostic accuracy. CONCLUSION: The molecular 5-gene score is associated with outcomes of patients with HCC treated by resection in different clinical settings worldwide. This new biomarker should be tested in clinical trials to stratify patients in therapeutic decision.

Antiviral therapy after curative treatment of hepatitis B/C virus-related hepatocellular carcinoma: A systematic review of randomized trials.

AIM: Available literature on the benefit of adjuvant antiviral therapy after curative treatment of hepatocellular carcinoma (HCC) reports controversial results. The objective of this systematic review was to evaluate the effect of adjuvant antiviral therapy on recurrence and survival after curative treatment of HCC. METHODS: We conducted an extensive search strategy. All randomized controlled trials comparing adjuvant antiviral therapy versus placebo or no treatment were considered for this review. Results were expressed as Hazard Ratio for time-to-event outcomes with 95% confidence intervals using RevMan 5. RESULTS: We included 9 trials (3 of low risk of bias and 6 of unclear risk of bias) with 954 patients. All the included studies used conventional interferon (IFN) as adjuvant antiviral therapy; none of them used pegylated IFN or nucleoside analogues. There were significant improvements for recurrence-free survival and overall survival in adjuvant IFN group compared with control group. Subgroup analysis also
showed a significant difference favoring IFN therapy in hepatitis C virus (HCV) related HCC patients, but for hepatitis B virus (HBV) related patients, the difference failed to reach statistical significance. A dose reduction was needed in 28.3% patients and discontinuation of IFN therapy happened in 8.2% patients due to moderate to severe side effects. CONCLUSION: Our study suggested potential benefits of adjuvant IFN therapy following curative treatment of HCC, especially for HCV-related HCC. Further high-quality randomized controlled trials of more effective adjuvant antiviral regimens, either used alone or in combination, for virus-related HCC, especially HBV-related HCC, are needed.


GOALS: To elucidate whether long-term supplementation with branched-chain amino acid (BCAA) granules improves overall survival (OS) and recurrence-free survival (RFS) after radiofrequency thermal ablation (RFA) in patients with hepatitis C virus (HCV)-related hepatocellular carcinoma (HCC) ≤3 cm in diameter with up to 3 nodules and a serum albumin level before RFA of ≤3.5 g/dL. BACKGROUND: Whether BCAA treatment after curative RFA for patients with HCV-related HCC improves OS and RFS remains unclear. STUDY: We compared the OS rate and the RFS rate between the BCAA group (n=115) and the control group (n=141). We also examined factors contributing to OS and RFS. RESULTS: The 1 and 3 years OS rates after RFA were 94.0% and 70.0%, respectively, in the BCAA group, and 94.0% and 49.8%, respectively, in the control group (P=0.001). The corresponding RFS rates 1 and 3 years after RFA were 61.8% and 28.0%, respectively, in the BCAA group, and 52.0% and 12.0%, respectively, in the control group (P=0.013). In the multivariate analysis, in terms of OS, BCAA treatment, and serum albumin level of ≥3.4 g/dL, and in terms of RFS, age 70 years or older, BCAA treatment, and a serum albumin level of ≥3.4 g/dL were significant independent factors, respectively. CONCLUSIONS: BCAA treatment may improve OS and RFS after RFA in patients with HCV-related HCC ≤3 cm in diameter with up to 3 nodules and a serum albumin level before RFA of 3.5 g/dL.


PURPOSE: To describe outcomes of prospective trials of stereotactic body radiotherapy (SBRT) for hepatocellular carcinoma (HCC). PATIENTS AND METHODS: Two trials of SBRT for patients with active HCC unsuitable for standard locoregional therapies were conducted from 2004 to 2010. All patients had Child-Turcotte-Pugh class A disease, with at least 700 mL of non-HCC liver. The SBRT dose range was 24 to 54 Gy in six fractions. Primary end points were toxicity and local control at 1 year (LC1y), defined as no progressive disease (PD) of irradiated HCC by RECIST (Response Evaluation Criteria in Solid Tumors). RESULTS: n = 50; Trial 2, 2007 to 2010: n = 52. Underlying liver disease was hepatitis B in 38% of patients, hepatitis C in 38%, alcohol related in 25%, other in 14%, and none in 7%. Fifty-two percent received prior therapies (no prior sorafenib). TNM stage was III in 66%, and 61% had multiple
lesions. Median gross tumor volume was 117.0 mL (range, 1.3 to 1,913.4 mL). Tumor vascular thrombosis (TVT) was present in 55%, and extrahepatic disease was present in 12%. LC1y was 87% (95% CI, 78% to 93%). SBRT dose (hazard ratio [HR] = 0.96; P = .02) and being in Trial 2 (HR = 0.38; P = .03) were associated with LC1y on univariate analysis. Toxicity ≥ grade 3 was seen in 30% of patients. In seven patients (two with TVT PD), death was possibly related to treatment (1.1 to 7.7 months after SBRT). Median overall survival was 17.0 months (95% CI, 10.4 to 21.3 months), for which only TVT (HR = 2.47; P = .01) and being in Trial 2 (HR = 0.49; P = .01) were significant on multivariate analysis. **CONCLUSION:** These results provide strong rationale for studying SBRT for HCC in a randomized trial.