



Caring Ambassadors Program Hepatitis C Newsletter

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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

An Integrated Alcohol Abuse and Medical Treatment Model for Patients with Hepatitis C.

Proeschold-Bell RJ, Patkar AA, et al. Dig Dis Sci. 2011 Dec 2. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22134784>

BACKGROUND: Patients with chronic hepatitis C virus (HCV) infection have high rates of alcohol consumption, which is associated with progression of fibrosis and lower response rates to HCV treatment. **AIMS:** This prospective cohort study examined the feasibility of a 24-week integrated alcohol and medical treatment to HCV-infected patients. **METHODS:** Patients were recruited from a hepatology clinic if they had an Alcohol Use Disorders Identification Test score >4 for women and >8 for men, suggesting hazardous alcohol consumption. The integrated model included patients receiving medical care and alcohol treatment within the same clinic. Alcohol treatment consisted of 6 months of group and individual therapy from an addictions specialist and consultation from a study team psychiatrist as needed. **RESULTS:** Sixty patients were initially enrolled, and 53 patients participated in treatment. The primary endpoint was the Addiction Severity Index (ASI) alcohol composite scores, which significantly decreased by 0.105 (41.7% reduction) between 0 and 3 months ($P < 0.01$) and by 0.128 (50.6% reduction) between 0 and 6 months ($P < 0.01$) after adjusting for covariates. Alcohol abstinence was reported by 40% of patients at 3 months and 44% at 6 months. Patients who did not become alcohol abstinent had reductions in their ASI alcohol composite scores from 0.298 at baseline to 0.219 (26.8% reduction) at 6 months ($P = 0.08$). **CONCLUSION:** This study demonstrated that an integrated model of alcohol treatment and medical care could be successfully implemented in a hepatology clinic with significant favorable impact on alcohol use and abstinence among patients with chronic HCV.

Weight loss and resting energy expenditure in patients with chronic hepatitis C before and during standard treatment.

Fioravante M, Alegre SM, Marin DM, Lorena SL, Seva Pereira T, Soares EC. Nutrition. 2011 Dec 22. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22196981>

OBJECTIVE: Infection with hepatitis C virus (HCV) is a serious public health problem worldwide. In clinical studies, weight loss has been reported in 11% to 29% of patients treated with pegylated interferon- α -2a/2b. Few reports have tried to explain such a weight loss. The aim of this study was to evaluate nutritional status, body composition, and resting energy expenditure

(REE) in patients with chronic hepatitis C before and during treatment with pegylated interferon and ribavirin. **METHODS:** This was a prospective study with the evaluation of patients with hepatitis C virus before and after 12 wk of treatment with pegylated interferon and ribavirin. The evaluation consisted of anthropometry (weight, height, body mass index, and waist circumference), and body composition was determined by bioelectrical impedance analysis. The REE of each individual was obtained by indirect calorimetry. To compare the two phases of treatment, the Wilcoxon test was used. The significance level was 5%. **RESULTS:** Subjects had significant weight loss during treatment with a consequent decrease in body mass index. This weight decrease was accompanied by a significant decrease in body fat and no decrease in fat-free mass. There was a significant decrease in energy intake as assessed by 24-h recall. However, there was no change in REE and in REE corrected for fat-free mass. **CONCLUSION:** Our study of patients with hepatitis C treatment showed that these patients had significant weight loss and this was not associated with changes in energy expenditure. However, we observed a significant decrease in energy intake, pointing to a possible need for intervention measures to decrease the damage.

Predicting cirrhosis and clinical outcomes in patients with advanced chronic hepatitis C with a panel of genetic markers (CRS7). Curto TM, Lagier RJ, Lok AS, et al. *Pharmacogenet Genomics*. 2011 Dec;21(12):851-60.

<http://www.ncbi.nlm.nih.gov/pubmed/21946897>

OBJECTIVES: Genetic factors may play a role in fibrosis progression in patients with chronic hepatitis C (CHC). A cirrhosis risk score (CRS7) with seven single nucleotide polymorphisms was previously shown to correlate with cirrhosis in patients with CHC. This study aimed to assess the validity of CRS7 as a marker of fibrosis progression and cirrhosis and as a predictor of clinical outcomes in patients with CHC. **METHODS:** A total of 938 patients (677 Caucasians, 165 African-Americans, and 96 Hispanic/Other) in the Hepatitis C Antiviral Long-term Treatment against Cirrhosis Trial were studied. CRS7 was categorized a priori as high risk (n=440), medium risk (n=310), or low risk (n=188). Patients were assessed for four possible outcomes: fibrosis progression, cirrhosis, clinical outcomes [decompensation or hepatocellular carcinoma (HCC)], or HCC alone. **RESULTS:** Twenty-nine percent (142/493) developed an increase in fibrosis score by greater than or equal to 2 points on follow-up biopsies, 58% had cirrhosis on one or more biopsies, 35% developed at least one clinical outcome, and 13% developed HCC. CRS7 (trend test) was associated with risk for fibrosis progression (P=0.04) with adjusted hazard ratio of 1.27 (95% confidence interval: 1.01-1.58) and with cirrhosis (P=0.05) with adjusted odds ratio of 1.19 (1.00-1.41). Rates of HCC and clinical outcomes were increased in patients with higher CRS7 scores, but were not statistically significant (P=0.12 clinical outcomes, and P=0.07 HCC). A single nucleotide polymorphism in AZIN1 was significantly associated with fibrosis progression. **CONCLUSION:** CRS7 was validated as a predictor of fibrosis progression and cirrhosis among Hepatitis C Antiviral Long-term Treatment against Cirrhosis patients, who all had advanced fibrosis. CRS7 was not predictive of clinical outcome.

Depressive symptoms in patients with hepatitis C treated with pegylated interferon alpha therapy: a 24-week prospective study. Pavlović Z, Delić D, Marić NP, Vuković O, Jašović-Gašić M. *Psychiatr Danub.* 2011 Dec;23(4):370-7.

<http://www.ncbi.nlm.nih.gov/pubmed/22075738>

OBJECTIVE: To prospectively evaluate depressive symptoms and risk factors for depression in patients with chronic hepatitis C (CHC) treated with pegylated interferon alpha therapy combined with oral ribavirin (PEG-IFN- α +RBV) and to analyze self-rating scale for depression in comparison to observer-based scale in the given population. **SUBJECTS AND METHODS:** The Hamilton Depression Rating Scale and Zung Self Rating Depression Scale were used to screen for depressive symptoms in 74 subjects with CHC before PEG-IFN- α (mean dose 152.6 \pm 25.6 mcg), and in the follow-up visits (4, 12 and 24 week). **RESULTS:** Incidence of depressive symptoms in patients (mean age 39.9 \pm 13.4 years; equal sex distribution p=0.225) treated by PEG-IFN- α was the highest on 12th week of the treatment, when more than a 20% of our sample had moderate/severe symptoms of depression, and about 30% had minor depressive symptoms. For the screening of depression during PEG-IFN- α self-assessment scale was equally reliable as observer-based assessment of depressive symptoms. Common clinical parameters-subject related risk factors (age (p=0.955), sex (p=0.008), lifetime psychiatric disorder (p=0.656)), illness related risk factors (duration of CHC (p=0.267), i.v drug application as way of transmission (p=0.292)) and therapy-related risk factors (recommended duration of PEG-IFN- α (p=0.993) and dose of PEG-IFN- α (p=0.841)) were not significantly associated with depressive symptoms on PEG-IFN- α . **CONCLUSIONS:** Liaison-consultation services should collaborate with hepatologists in creating screening programmes, supplemented by objective criteria and guidelines, for early recognition and treatment of interferon-induced depression.

Hepatic steatosis at 1 year is an additional predictor of subsequent fibrosis severity in liver transplant recipients with recurrent hepatitis C virus. Brandman D, Pingitore A, Lai JC, Roberts JP, Ferrell L, Bass NM, Terrault NA. *Liver Transpl.* 2011 Dec;17(12):1380-6. doi: 10.1002/lt.22389.

<http://www.ncbi.nlm.nih.gov/pubmed/21770018>

Recurrent hepatitis C virus (HCV) is the most common cause of graft loss for HCV-infected recipients of liver transplantation (LT). Diabetes mellitus (DM) has been associated with increased rates of fibrosis progression, but whether steatosis affects post-LT outcomes independently of DM is unclear. Using a retrospective cohort of HCV-infected LT recipients, we determined the prevalence of hepatic steatosis and evaluated the relationship between steatosis on index biopsy 1 year after LT (\pm 6 months) and the severity of the subsequent fibrosis. One hundred fifty-two LT recipients with HCV were followed up for a median of 2.09 years (range = 0.13-6.17 years) after index biopsy; the median number of biopsy procedures per patient after index biopsy was 2 (range = 1-6). Steatosis (\geq 5%) was present in 45 individuals (29.6%) according to index biopsy samples taken 1 year after LT; the steatosis was mild (grade 1) in 80% of the patients. In the multivariate analysis, the presence of steatosis 1 year after LT was positively associated with HCV genotype 3 [odds ratio (OR) = 3.60, P = 0.02], older donor age (OR = 1.03, P = 0.04), and pre-LT hypertension (OR = 3.29, P = 0.009). Two years after index biopsy, the cumulative rate of significant fibrosis (F2-F4 on the Ludwig-Batts scale) was 49% in the patients with steatosis at 1 year and 24% in the patients without steatosis (P = 0.003). In the multivariate analysis, steatosis at 1 year was an independent predictor of subsequent F2 to F4 fibrosis (HR = 2.63, 95% CI = 1.49-4.63). Steatosis was a stronger predictor of fibrosis in the

setting of sirolimus use (hazard ratio = 9.38, 95% confidence interval = 1.37-64.16, P = 0.02). **In conclusion**, steatosis is frequent in the early post-LT period, and steatosis within the first year after LT is a marker of a higher risk of fibrosis progression in HCV-infected patients.

A randomized controlled trial of rituximab following failure of antiviral therapy for hepatitis C-associated cryoglobulinemic vasculitis. Sneller MC, Hu Z, Langford CA. *Arthritis Rheum.* 2011 Dec 6. doi: 10.1002/art.34322. [Epub ahead of print]
<http://www.ncbi.nlm.nih.gov/pubmed/22147444>

OBJECTIVES: To report on the results of a randomized controlled trial of rituximab in hepatitis C virus (HCV)-associated mixed cryoglobulinemic vasculitis. **METHODS:** We conducted an open-label single center randomized controlled trial of rituximab (375 mg/m²) per week for 4 weeks) compared to best available therapy for treatment of patients with HCV-associated cryoglobulinemic vasculitis in whom antiviral therapy failed to induce remission. The primary endpoint was remission at 6 months from study entry. **RESULTS:** A total of 24 patients were enrolled. Baseline disease activity and organ involvement were similar in the two groups. Ten patients in the rituximab group (83%) were in remission at study month 6, compared with 1 patient in the control group (8%), a result that met criterion for stopping the study (P<0.001). The median duration of remission for rituximab-treated patients reaching the primary endpoint was 7 months. No adverse effect of rituximab on HCV plasma viremia or hepatic transaminase levels was observed. **CONCLUSIONS:** Therapy with rituximab was well tolerated and effective treatment for patients with HCV-associated cryoglobulinemic vasculitis in whom antiviral therapy fails to induce remission.

Multiple ascending dose study of BMS-790052, a nonstructural protein 5A replication complex inhibitor, in patients infected with hepatitis C virus genotype 1. Nettles RE, Gao M, Bifano M, et al. *Hepatology.* 2011 Dec;54(6):1956-65. doi: 10.1002/hep.24609.
<http://www.ncbi.nlm.nih.gov/pubmed/21837752>

The antiviral activity, resistance profile, pharmacokinetics (PK), safety, and tolerability of BMS-790052, a nonstructural protein 5A (NS5A) replication complex inhibitor, were evaluated in a double-blind, placebo-controlled, sequential panel, multiple ascending dose study. Thirty patients with chronic hepatitis C virus (HCV) genotype 1 infection were randomized to receive a 14-day course of BMS-790052 (1, 10, 30, 60, or 100 mg once daily or 30 mg twice daily) or placebo in a ratio of 4:1. The mean maximum decline from baseline in HCV RNA ranged from 2.8 to 4.1 log₁₀ IU/mL; the placebo group showed no evidence of antiviral activity. Most patients experienced viral rebound on or before day 7 of treatment with BMS-790052 monotherapy; viral rebound was associated with viral variants that had been previously implicated in resistance development in the in vitro replicon system. The PK profile was supportive of once-daily dosing with median peak plasma concentrations at 1-2 hours postdose and mean terminal half-life of 12-15 hours. Steady state was achieved following 3-4 days of daily dosing. BMS-790052 was well tolerated in all dose groups, with adverse events occurring with a similar frequency in BMS-790052- and placebo-treated groups. There were no clinically relevant changes in vital signs, laboratory, or electrocardiogram parameters. **CONCLUSION:** BMS-7590052 is the first NS5A replication complex inhibitor with multiple dose proof-of-concept in clinic. At doses of 1-100 mg daily, BMS-790052 was well tolerated, had a PK profile supportive of once-daily dosing, and produced a rapid and substantial decrease in HCV-RNA levels in patients chronically infected with HCV genotype 1.

African Americans Are Less Likely to Have Clearance of Hepatitis C Virus Infection: The Findings from Recent U.S. Population Data. Mir HM, Stepanova M, Afendy M, Kugelmas M, Younossi ZM. *J Clin Gastroenterol.* 2011 Dec 14. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22178959>

BACKGROUND: Hepatitis C virus (HCV) is the most common cause of chronic liver disease in the United States. African Americans are known to have a higher prevalence of HCV and lower response to anti-HCV therapy. **GOAL:** The aim of this study is to assess the differences in the prevalence of chronic HCV infection in according to patients' ethnic background. **STUDY:** We used the recent National Health and Nutrition Examination Survey with extensive clinical and laboratory data. Active HCV infection was defined as having HCV-positive antibody with detectable HCV RNA by polymerase chain reaction. HCV clearance was defined as HCV-positive antibody with negative HCV RNA. Clinico-demographic data were compared between anti-HCV positive individuals with or without HCV clearance. The stratum-specific χ test for independence was used. Logistic regression was used to identify independent predictors of HCV clearance. P-values ≤ 0.05 were considered statistically significant. All analyses were run using SAS 9.1 and SUDAAN 10.0. **RESULTS:** The cohort included 14,750 adults (age 47.6 ± 0.75 y, 64% white, 21% African American, 10% Hispanics, and 63% male). Of these, $1.32 \pm 0.11\%$ were anti-HCV positive with $75.94 \pm 4.72\%$ having active HCV viremia. The only parameter significantly different between those who did or did not clear HCV was the proportion of African Americans: $8.0 \pm 3.7\%$ versus $24.9 \pm 5.0\%$, $P=0.0163$. Indeed, the rate of HCV clearance was lowest among African Americans ($9.3 \pm 3.5\%$) as compared with both whites ($27.2 \pm 6.5\%$) and Hispanics $31.2 \pm 9.1\%$ ($P < 0.05$). In multivariate analysis, the only independent predictor of active HCV infection was African American race: odds ratio (95% confidence interval) = 3.80 ($1.31-11.06$), $P=0.0151$. **CONCLUSIONS:** African Americans not only have lower response to anti-HCV therapy but also are less likely to naturally clear HCV, potentially contributing to higher prevalence of HCV.

Weight-based high- and low-dose ribavirin in combination with peginterferon α -2b therapy for genotype 2 chronic hepatitis C: A randomized trial. Kagawa T, Kojima SI, Shiraishi K, et al. *Hepatol Res.* 2011 Dec 16. doi: 10.1111/j.1872-034X.2011.00944.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22176474>

AIM: The optimal ribavirin dose in the treatment of patients infected with hepatitis C virus (HCV) genotype 2 remains to be elucidated. We aimed to seek the optimal ribavirin dose required for this genotype in a randomized trial. **METHODS:** We compared the efficacy and tolerability of the 24-week peginterferon α -2b ($1.5 \mu\text{g/kg/week}$) therapy in combination with a weight-based higher dose ($600-1000 \text{ mg}$) and lower dose ($400-800 \text{ mg}$) of ribavirin for genotype 2 patients. Noninferior margin was set at 10%. **RESULTS:** A total of 120 patients were randomized to a higher-dose or a lower-dose group. Sustained virological response (SVR) by intention-to-treat analysis was achieved in $47/58$ (81.0% , 90% confidential interval [CI]: $72.6-89.5$) patients in the higher-dose group and $41/60$ (68.3% , 90% CI: $58.5-78.2$) patients in the lower-dose group (difference, -12.7% ; 90% CI, -25.7 to 0.3). Relapse rates were 10% and 21.6% in the higher-dose and the lower-dose groups, respectively. Multiple logistic regression analysis showed that ribavirin dose/kg body weight was the only significant predictor of SVR ($\geq 9.5 \text{ mg/kg per day}$ vs $< 9.5 \text{ mg/kg per day}$; odds ratio = 3.34 ; 95% CI, $1.41-7.92$; $P = 0.006$). Twenty-one (36.2%) in the higher-dose group required ribavirin dose reduction because

of anemia, whereas seven patients (11.7%) did in the lower-dose group ($P < 0.01$). Three of the higher-dose group and two of the lower-dose group required premature termination of therapy. **CONCLUSIONS:** Weight-based lower-dose ribavirin regimen was not equivalent to the higher-dose counterpart in the treatment of HCV genotype 2. We discourage treating these patients with low-dose ribavirin regimens. The peginterferon therapy in combination with ribavirin at a weight-based higher dose (600-1000 mg) remains the standard-of-care treatment for this genotype.

Interleukin (IL)-17/IL-22-Producing T cells Enriched Within the Liver of Patients with Chronic Hepatitis C Viral (HCV) Infection. Foster RG, Golden-Mason L, Rutebemberwa A, Rosen HR. Dig Dis Sci. 2011 Dec 20. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22183819>

BACKGROUND: Effector CD4+ helper T cells have historically been classified into T helper 1 (Th1) and Th2 based on the production of signature cytokines. The recently identified interleukin (IL)-17 cytokine family plays important roles in host immunity against intracellular pathogens and in chronic inflammatory conditions; data have implicated IL-17 in autoimmune and viral liver disease. **METHODS:** This study used three patient groups with HCV infection: acute HCV who either cleared spontaneously or became chronically infected ($n = 12$), endstage liver disease from whom both peripheral and intrahepatic lymphocytes were studied directly ex vivo ($n = 11$), and 134 patients with different stages of HCV-related fibrosis from whom serum was collected concurrently with liver biopsy. Normal healthy subjects ($n = 41$) served as controls. **RESULTS:** Acute HCV was not associated with expansion of either CD4+ or CD8+ T cells producing IL-17 (Th17, Tc17) or IL-22, and frequencies did not differ in the blood of patients who cleared versus became persistently infected. The hepatic compartment of chronic HCV patients demonstrated statistically more CD4+ and CD8+ that produced IL-17, IL-22 or both as compared to peripheral blood. These T cells displayed a distinct phenotypic profile, high expression of the homing receptor CD161 and low levels of inhibitory receptors, mucin-domain-containing-molecule-3 (Tim-3) and programmed-death 1. Using a sensitive ELISA, we found no significant differences in serum levels of IL-17 according to HCV-related fibrosis. **CONCLUSIONS:** In chronic HCV, T cells producing IL-17/IL-22 may home to the liver; however, circulating levels of IL-17 do not correlate with fibrosis.

Occurrence of clinical depression during combination therapy with pegylated interferon alpha or natural human interferon beta plus ribavirin. Nomura H, Miyagi Y, Tanimoto H, Yamashita N, Oohashi S, Nishiura S. Hepatol Res. 2011 Dec 16. doi: 10.1111/j.1872-034X.2011.00930.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22176275>

AIM: The onset of depression symptoms during pegylated interferon α plus ribavirin (PEG-IFN/RBV) combination therapy has led to treatment discontinuation in some cases. In the present study, we conducted a questionnaire survey during treatment to determine whether natural human interferon β plus ribavirin (IFN β /RBV) therapy is associated with a lower incidence of depression symptom onset compared with PEG-IFN/RBV therapy. **METHODS:** Seventy-seven patients with chronic hepatitis C received PEG-IFN/RBV (PR) or IFN β /RBV (FR) therapy. A questionnaire survey was administered at the start of treatment, and at 4 and 12 weeks, using the Beck Depression Inventory II (BDI-II) and the Pittsburgh Sleep Quality Index (PSQI). **RESULTS:** BDI-II scores in the PR group increased at 4 and 12 weeks, but remained

unchanged in the FR group. At 12 weeks, the mean BDI-II score and incidence of abnormalities with a BDI-II score of ≥ 14 were significantly lower in the FR group than in the PR group. BDI-II scores during IFN β /RBV therapy in 11 patients currently using antidepressants remained unchanged up to 12 weeks. None of these 11 patients required addition or dose increases of antidepressants, and there was no evidence of worsened depression symptoms. Nine PR patients had BDI-II scores of ≥ 14 and PSQI scores of ≥ 11 at 12 weeks. **CONCLUSIONS:** IFN β /RBV therapy was associated with a lower incidence of depression symptom onset during treatment. In patients already diagnosed with depression, there was no evidence that IFN β /RBV therapy caused any worsening of symptoms, indicating that IFN β /RBV therapy is safe for patients with depression.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

In vitro characterization of the activity of PF-05095808 a novel biological agent for Hepatitis C Virus therapy. Lavender H, Brady K, Burden F, et al. *Antimicrob Agents Chemother.* 2011 Dec 27. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22203606>

PF-05095808 is a novel biological agent for chronic Hepatitis C Virus (HCV) therapy. It comprises a recombinant Adeno-associated virus (AAV) DNA vector packaged into an AAV serotype 8 capsid. The vector directs expression of 3 short hairpin (sh) RNAs targeted to conserved regions of the HCV genome. These shRNAs are processed by the host cell into the small interfering RNAs which mediate sequence specific cleavage of target regions. For small molecule inhibitors the key screens needed to assess in vitro activity are well defined, we developed new assays to assess this RNA interference agent and so understand its therapeutic potential. Following administration of PF-05095808 or corresponding synthetic shRNAs, sequence specific antiviral activity was observed in HCV replicon and infectious virus systems. To quantify the numbers of shRNA molecules required for antiviral activity in vitro and potentially also in vivo, a universal qPCR assay was developed. The number of shRNA molecules needed to drive antiviral activity proved independent of the vector delivery system used for PF-05095808 administration. The emergence of resistant variants at the target site of one shRNA was characterised. A novel RNA cleavage assay was developed to confirm the spectrum of activity of PF-05095808 against common HCV clinical isolates. **In summary**, our data supports both antiviral activity consistent with an RNA interference mechanism and demonstrates the potential of PF-05095808 as a therapeutic agent for chronic HCV infection.

Characterization of Resistance to the Non-Nucleoside NS5B Inhibitor Filibuvir in Hepatitis C Infected Patients. Troke PJ, Lewis M, Simpson P, Gore K, Hammond J, Craig C, Westby M. *Antimicrob Agents Chemother.* 2011 Dec 27. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22203605>

Filibuvir (PF-00868554) is an investigational non-nucleoside inhibitor of the hepatitis C virus (HCV) non-structural 5B (NS5B) RNA-dependent RNA polymerase, currently in development for treating chronic HCV infection. The aim of this study was to characterize the selection of filibuvir-resistant variants in HCV-infected individuals receiving filibuvir as short (3-10 days) monotherapy. We identified amino acid M423 as the primary site of mutation arising upon filibuvir dosing. Through bulk cloning of clinical NS5B sequences into a transient replicon system, and supported by site-directed mutagenesis of the Con1 replicon, we confirmed that

mutations M423I/T/V mediate phenotypic resistance. Selection in patients of an NS5B mutation at M423 was associated with a reduced replicative capacity in vitro relative to the pre-therapy sequence; consistent with this, reversion towards wild-type M423 was observed in the majority of patients following therapy cessation. Mutations at NS5B residues R422 and M426 were detected in a small number of patients at baseline or end of therapy, and also mediate reductions in filibuvir susceptibility, suggesting these are rare but clinically relevant alternative resistance pathways. Amino acid variants at position M423 in HCV NS5B polymerase are the preferred pathway for selection of viral resistance to filibuvir in vivo.

HAVCR1 gene haplotypes and infection by different viral hepatitis C virus genotypes.

Abad-Molina C, Garcia-Lozano JR, Montes-Cano MA, et al. Clin Vaccine Immunol. 2011 Dec 21. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22190394>

The HAVCR1 gene is highly polymorphic and several variants have been associated with susceptibility to allergic and autoimmune diseases. The HAVCR1 region was identified as a candidate for hepatitis C virus (HCV) natural clearance in a genotyping study of selected immune response genes in both the European-American and African-American populations. The aim of the present study was to explore the influence of HAVCR1 in the outcome of HCV infection in the Spanish population. Two cohorts consisting of 354 subjects (285 with persistent HCV mono-infection and 69 with natural clearance) and 182 co-infected HIV/HCV patients, and 320 controls were included. Samples were genotyped in several polymorphic positions: insertion/deletion variants in the exon 4 and tag SNPs, in order to define previously described HAVCR1 haplotypes (haplotypes A-D). No statistically significant differences were observed with spontaneous resolution of infection nor with viral clearance after treatment. Nevertheless, different rates of infection by viral genotypes (G) among the HAVCR1 haplotypes were observed. Individuals bearing haplotype C had the highest viral G1 infection rate when comparing with the rest of individuals (75.82% vs. 57.72%, $p=3.2 \times 10^{-4}$, OR=2.30, 95% CI=1.51-3.47). Thus, HAVCR1 could be involved in susceptibility or resistance to the infection by a particular HCV genotype.

The CXCL1 rs4074 A allele is associated with enhanced CXCL1 responses to TLR2 ligands and predisposes to cirrhosis in HCV genotype 1-infected Caucasian patients.

Nischalke HD, Berger C, Luda C, et al. J Hepatol. 2011 Dec 13. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22173151>

BACKGROUND & AIMS: CXCL1 is a ligand for CXC chemokine-receptor 2 expressed on hepatic stellate cells (HSC). Thus, CXCL1 might contribute to HSC activation and fibrogenesis. Here, we investigated, whether the CXCL1 rs4074 polymorphism affects CXCL1 expression and progression of chronic hepatitis C virus (HCV) infection towards cirrhosis. **METHODS:** The study involved 237 patients with chronic HCV genotype 1 infection (75 with cirrhosis) and 342 healthy controls. The CXCL1 rs4074 polymorphism was determined by a LightSNiP assay on the LightCycler system. CXCL1 serum levels and induction in response to HCV proteins were studied by ELISA. **RESULTS:** Distributions of CXCL1 genotypes (GG/GA/AA) matched the Hardy-Weinberg equilibrium in all subgroups (HCV-associated cirrhosis: 29.3%/54.7%/16.0%; non-cirrhotic HCV infection: 45.1%/44.4%/10.5%, healthy controls: 46.2%/40.9%/12.9%). HCV-infected cirrhotic patients had a significantly greater CXCL1 rs4074 A allele frequency (43.3%) than patients without cirrhosis (32.7%, OR=1.573, $p=0.03$) and healthy controls (33.3%),

OR=1.529, p=0.02). In vitro carriers of the A allele produced greater amounts of CXCL1 in response to TLR2-ligands including HCV core and NS3, and HCV-infected carriers of the CXCL1 rs4074 A allele had higher CXCL1 serum levels than those with the G/G genotype. Moreover, multivariate Cox-regression analysis confirmed age and the presence of a CXCL1 rs4074 A allele as risk factors for cirrhosis. **CONCLUSIONS:** Enhanced production of CXCL1 in response to HCV antigens in carriers of the rs4074 A allele together with its increased frequency in cirrhotic patients with hepatitis C suggest the CXCL1 rs4074 A allele as a genetic risk factor for cirrhosis progression in hepatitis C.

Molecular signatures of peripheral blood mononuclear cells during chronic interferon- α treatment: relationship with depression and fatigue. Felger JC, Cole SW, Pace TW, et al.

Psychol Med. 2011 Dec 9:1-13. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22152193>

BACKGROUND: Interferon-alpha (IFN- α) treatment for infectious disease and cancer causes high rates of depression and fatigue, and has been used to investigate the impact of inflammatory cytokines on brain and behavior. However, little is known about the transcriptional impact of chronic IFN- α on immune cells in vivo and its relationship to IFN- α -induced behavioral changes.

METHOD: Genome-wide transcriptional profiling was performed on peripheral blood mononuclear cells (PBMCs) from 21 patients with chronic hepatitis C virus (HCV) either awaiting IFN- α therapy (n=10) or at 12 weeks of IFN- α treatment (n=11). **RESULTS:** Significance analysis of microarray data identified 252 up-regulated and 116 down-regulated gene transcripts. Of the up-regulated genes, 2'-5'-oligoadenylate synthetase 2 (OAS2), a gene linked to chronic fatigue syndrome (CFS), was the only gene that was differentially expressed in patients with IFN- α -induced depression/fatigue, and correlated with depression and fatigue scores at 12 weeks (r=0.80, p=0.003 and r=0.70, p=0.017 respectively). Promoter-based bioinformatic analyses linked IFN- α -related transcriptional alterations to transcription factors involved in myeloid differentiation, IFN- α signaling, activator protein-1 (AP1) and cAMP responsive element binding protein/activation transcription factor (CREB/ATF) pathways, which were derived primarily from monocytes and plasmacytoid dendritic cells. IFN- α -treated patients with high depression/fatigue scores demonstrated up-regulation of genes bearing promoter motifs for transcription factors involved in myeloid differentiation, IFN- α and AP1 signaling, and reduced prevalence of motifs for CREB/ATF, which has been implicated in major depression.

CONCLUSIONS: Depression and fatigue during chronic IFN- α administration were associated with alterations in the expression (OAS2) and transcriptional control (CREB/ATF) of genes linked to behavioral disorders including CFS and major depression, further supporting an immune contribution to these diseases.

Serum leptin and ghrelin in chronic hepatitis C patients with steatosis. Pavlidis C, Panoutsopoulos GI, Tiniakos D, et al. World J Gastroenterol. 2011 Dec 14;17(46):5097-104.

<http://www.ncbi.nlm.nih.gov/pubmed/22171144>

AIM: To determine the associations between leptin and ghrelin concentrations and sustained virological response (SVR) in chronic hepatitis C patients with steatosis. **METHODS:** We retrospectively assessed 56 patients infected with hepatitis C virus (HCV) genotype-1 and 40 with HCV genotype-3. Patients with decompensated cirrhosis, and those with other causes of chronic liver disease, were excluded. Serum HCV-RNA concentrations were measured before the initiation of treatment; at weeks 12 (for genotype 1 patients), 24 and 48 during treatment; and

24 wk after the end of treatment. Genotype was determined using INNO-LIPA HCV assays, and serum leptin and ghrelin concentrations were measured using enzyme-linked immunosorbent assay. Biopsy specimens were scored according to the Ishak system and steatosis was graded as mild, moderate, or severe, according to the Brunt classification. **RESULTS:** Overall, SVR was positively related to the presence of genotype-3, to biopsy-determined lower histological stage of liver disease, and lower grade of steatosis. Patients ≥ 40 years old tended to be less responsive to therapy. In genotype-1 infected patients, SVR was associated with a lower grade of liver steatosis, milder fibrosis, and an absence of insulin resistance. Genotype-1 infected patients who did not achieve SVR had significantly higher leptin concentrations at baseline, with significant increases as the severity of steatosis worsened, whereas those who achieved SVR had higher ghrelin concentrations. In genotype-3 infected patients, SVR was associated only with fibrosis stage and lower homeostasis model assessment insulin resistance at baseline, but not with the degree of steatosis or leptin concentrations. Genotype-3 infected patients who achieved SVR showed significant decreases in ghrelin concentration at end of treatment. Baseline ghrelin concentrations were elevated in responders of both genotypes who had moderate and severe steatosis. **CONCLUSION:** Increased serum leptin before treatment may predict non-SVR, especially in HCV genotype-1 infected patients, whereas increased ghrelin may predict SVR in genotype-1.

Normalizing for Individual Cell Population Context in the Analysis of high-content Cellular Screens. Knapp B, Rebhan I, Kumar A, et al. *MC Bioinformatics*. 2011 Dec 20;12(1):485. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22185194>

BACKGROUND: High-content, high-throughput RNA interference (RNAi) offers unprecedented possibilities to elucidate gene function and involvement in biological processes. Microscopy based screening allows phenotypic observations at the level of individual cells. It was recently shown that a cell's population context significantly influences results. However, standard analysis methods for cellular screens do not currently take individual cell data into account unless this is important for the phenotype of interest, i.e. when studying cell morphology. **RESULTS:** We present a method that normalizes and statistically scores microscopy based RNAi screens, exploiting individual cell information of hundreds of cells per knockdown. Each cell's individual population context is employed in normalization. We present results on two infection screens for hepatitis C and dengue virus, both showing considerable effects on observed phenotypes due to population context. In addition, we show on a non-virus screen that these effects can be found also in RNAi data in the absence of any virus. Using our approach to normalize against these effects we achieve improved performance in comparison to an analysis without this normalization and hit scoring strategy. Furthermore, our approach results in the identification of considerably more significantly enriched pathways in hepatitis C virus replication than using a standard analysis approach. **CONCLUSIONS:** Using a cell-based analysis and normalization for population context, we achieve improved sensitivity and specificity not only on a individual protein level, but especially also on a pathway level. This leads to the identification of new host dependency factors of the hepatitis C and dengue viruses and higher reproducibility of results.

HCV core and NS3 proteins manipulate human blood-derived dendritic cell development and promote Th 17 differentiation. Tu Z, Hamalainen-Laanaya HK, Nishitani C, et al.

<http://www.ncbi.nlm.nih.gov/pubmed/22190574>

Hepatitis C virus (HCV) chronic infection is characterized by low-level or undetectable cellular immune response against HCV antigens. HCV proteins affect various intracellular events and modulate immune responses, although the mechanisms that mediate these effects are not fully understood. In this study, we examined the effect of HCV proteins on the differentiation of human peripheral blood monocytes to dendritic cells (DCs). The HCV core (HCVc) and non-structural 3 (NS3) proteins inhibited the expression of CD1a, CD1b and DC-SIGN during monocyte differentiation to DCs, while increasing some markers characteristic of macrophages (CD14 and HLA-DR) and also PD-L1 expression. Meanwhile, HCVc and NS3 could induce differentiating monocytes to secrete IL-10. However, anti-IL-10 mAb could not reverse HCVc and NS3 inhibition of monocyte differentiation into DCs. The HCVc and NS3 proteins increased IL-6 secretion both in immature and in fully differentiated DCs and also promoted CD4+ T-cell IL-17 production. Since T(h) 17 cells are active in many examples of immunopathology, these effects may contribute to HCV autoimmune responses in chronically infected patients.

Functional delivery of DNAzyme with iron oxide nanoparticles for hepatitis C virus gene knockdown. Ryoo SR, Jang H, Kim KS, et al. Biomaterials. 2011 Dec 27. [Epub ahead of print]

Lee B, Kim KB, Kim YK, Yeo WS, Lee Y, Kim DE, Min DH.

<http://www.ncbi.nlm.nih.gov/pubmed/22206595>

DNAzyme is an attractive therapeutic oligonucleotide which enables cleavage of mRNA in a sequence-specific manner and thus, silencing target gene. A particularly important challenge in achieving the successful down-regulation of gene expression is to efficiently deliver DNAzymes to disease sites and cells. Here, we report the nanoparticle-assisted functional delivery of therapeutic DNAzyme for the treatment of hepatitis C by inducing knockdown of hepatitis C virus (HCV) gene, NS3. HCV NS3 gene encodes helicase and protease which are essential for the virus replication. The nanocomplex showed efficient NS3 knockdown while not evoking undesired immune responses or notable cytotoxicity. We also demonstrated the DNAzyme conjugated nanoparticle system could be applicable in vivo by showing the accumulation of the nanoparticles in liver, and more specifically, in hepatocytes.

Hepatic cell-to-cell transmission of small silencing RNA can extend the therapeutic reach of RNA interference (RNAi). Pan Q, Ramakrishnaiah V, Henry S, et al. Gut. 2011 Dec 23. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22198713>

BACKGROUND/AIMS: RNA interference (RNAi), a sequence-specific gene silencing technology triggered by small interfering RNA (siRNA), represents promising new avenues for treatment of various liver diseases including hepatitis C virus (HCV) infection. In plants and invertebrates, RNAi provides an important mechanism of cellular defence against viral pathogens and is dependent on the spread of siRNA to neighbouring cells. A study was undertaken to investigate whether vector-delivered RNAi can transfer between hepatic cells in vitro and in mice, and whether this exchange could extend the therapeutic effect of RNAi against HCV infection. **METHODS:** Transmission of RNAi was investigated in culture by assessing silencing of HCV replication and expression of viral entry receptor CD81 using a human hepatic cell line and primary B lymphocytes transduced with siRNA-expressing vectors. In vivo

transmission between hepatic cells was investigated in NOD/SCID mice. Involvement of exosomes was demonstrated by purification, uptake and mass spectrometric analysis.

RESULTS: Human and mouse liver cells, as well as primary human B cells, were found to have the ability to exchange small RNAs, including cellular endogenous microRNA and delivered siRNA targeting HCV or CD81. The transmission of RNAi was largely independent of cell contact and partially mediated by exosomes. Evidence of RNAi transmission in vivo was observed in NOD/SCID mice engrafted with human hepatoma cells producing CD81 siRNA, causing suppression of CD81 expression in mouse hepatocytes. **CONCLUSION:** Both human and mouse hepatic cells exchange small silencing RNAs, partially mediated by shuttling of exosomes. Transmission of siRNA potentially extends the therapeutic reach of RNAi-based therapies against HCV as well as other liver diseases.

HIV/HCV COINFECTION

High plasma CXCL10 levels are associated with HCV-genotype 1, and higher insulin resistance, fibrosis, and HIV viral load in HIV/HCV coinfecting patients. Berenguer J, Fernandez-Rodríguez A, Jimenez-Sousa MA, et al. Cytokine. 2012 Jan;57(1):25-9. Epub 2011 Dec 3.

<http://www.ncbi.nlm.nih.gov/pubmed/22136974>

BACKGROUND: CXCL10 may contribute to the host immune response against the hepatitis C virus (HCV), liver disease progression, and response to HCV antiviral therapy. The aim of our study was to analyze the relationship among virological, immunological, and clinical characteristics with plasma CXCL10 levels in human immunodeficiency virus (HIV)/HCV-coinfecting patients. **METHODS:** We carried out a cross-sectional study on 144 patients. CXCL10 and insulin were measured using an immunoassay kit. The degree of insulin resistance was estimated for each patient using the homeostatic model assessment (HOMA) method. Insulin resistance was defined as a HOMA index higher than or equal to 3.8. Aspartate aminotransferase (AST) to platelet ratio (APRI), FIB-4, Forns index, HGM1, and HGM2 were calculated. **RESULTS:** The variables associated with log(10) CXCL10 levels by univariate analysis were age (b=0.013; p=0.023), prior AIDS-defining condition (b=0.127; p=0.045), detectable plasma HIV viral load (b=0.092; p=0.006), log(10) HOMA (b=0.216; p=0.002), HCV-genotype 1 (b=0.114; p=0.071), and liver fibrosis assessed by all non-invasive indexes (log(10) APRI (b=0.296; p=0.001), log(10) FIB-4 (b=0.436; p<0.001), log(10) Forns index (b=0.591; p<0.001), log(10) HGM1 (b=0.351; p=0.021), and log(10) HGM2 (b=0.215; p=0.018)). However, in multivariate analysis, CXCL10 levels were only associated with HOMA, detectable plasma HIV viral load, HCV-genotype 1 and FIB-4 (R-square=0.235; p<0.001). **CONCLUSION:** Plasma CXCL10 levels were influenced by several characteristics of patients related to HIV and HCV infections, insulin resistance, and liver fibrosis, indicating that CXCL10 may play an important role in the pathogenesis of both HCV and HIV infections.

Assessing mortality in women with hepatitis C virus and human immunodeficiency virus using indirect markers of fibrosis. Bambha K, Pierce C, Cox C, et al, AIDS. 2011 Dec 7.

[Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22156972>

Co-infection with hepatitis C (HCV) is a major cause of morbidity and mortality in HIV infected individuals. However, predictors of mortality are poorly defined and most studies have focused

predominantly on co-infection in men. **OBJECTIVES:** We evaluated whether two indirect markers of hepatic fibrosis, APRI and FIB-4 scores, were predictive of mortality in a well-defined longitudinal cohort of HCV/HIV co-infected women on HAART. **METHODS:** HCV/HIV co-infected women on antiretroviral therapy enrolled in Women's Interagency HIV Study (WIHS), an NIH funded prospective, multicenter, cohort study of women with and at risk for HIV infection were included. Using Cox regression analysis, associations between APRI and FIB-4 with all-cause mortality were assessed. **RESULTS:** 450 HCV/HIV co-infected women, of whom 191 women died, had a median follow up of 6.6 years and 5739 WIHS visits. Compared to women with low APRI or FIB-4 levels, severe fibrosis was significantly associated with an increased risk of all-cause mortality (APRI: 2.78 [95% CI 1.87, 4.12]; FIB-4 HR 2.58 [95% CI 1.68, 3.95]). Crude death rates per 1000 patient-years increased with increasing liver fibrosis: 34.8 for mild, 51.3 for moderate and 167.9 for severe fibrosis as measured by FIB-4. Importantly, both APRI and FIB-4 increased during the 5 years prior to death for all women: the slope of increase was greater for women dying a liver-related death compared to non-liver-related death. **CONCLUSION:** Both APRI and FIB-4 are independently associated with all-cause mortality in HCV/HIV co-infected women and may have clinical prognostic utility among women with HIV and HCV.

European mitochondrial DNA haplogroups and metabolic disorders in HIV/HCV-coinfected patients on highly active antiretroviral therapy. Micheloud D, Berenguer J, Guzmán-Fulgencio M, et al. *J Acquir Immune Defic Syndr.* 2011 Dec 1;58(4):371-8.

<http://www.ncbi.nlm.nih.gov/pubmed/21792063>

BACKGROUND: Mitochondrial DNA (mtDNA) haplogroups play an important role in susceptibility to metabolic disorders and cardiovascular disease. **METHODS:** We carried out a cross-sectional study in 248 HIV/hepatitis C virus-coinfected patients on highly active antiretroviral therapy to investigate whether mtDNA haplogroups had any influence on metabolic disorders. mtDNA genotyping was performed using the Sequenom MassARRAY platform. Insulin resistance (IR) was estimated using the homeostatic model assessment (HOMA) ($\text{HOMA} \geq 3.8$), which was calculated as fasting plasma glucose (mmol/L) times fasting serum insulin (mU/L) divided by 22.5. A high atherogenic risk was assessed when the atherogenic index (AI) was ≥ 3.5 . AI was calculated as total cholesterol (mg/dL) divided by HDL (mg/dL). **RESULTS:** The major haplogroup HV and haplogroup H had reduced odds ratios of IR ($\text{HOMA} \geq 3.8$) [0.45 (95% CI: 0.24 to 0.85) and 0.36 (95% CI: 0.18 to 0.69), respectively], and high AI ($\text{AI} \geq 3.5$) [0.44 (95% CI: 0.22 to 0.87) and 0.40 (95% CI: 0.19 to 0.80), respectively]. The major haplogroup U had increased odds of IR [2.66 (95% CI: 1.39 to 5.8)]. The major haplogroup JT and haplogroup T had increased odds of high AI [2.86 (95% CI: 1.29 to 6.33) and 4.01 (95% CI: 1.59 to 10.03), respectively]. Additionally, we found that patients belonging to the major haplogroup HV had lower values of serum hepatic growth factor and nerve growth factor, and higher values of adiponectin than patients belonging to the major haplogroup JT ($P < 0.05$). **CONCLUSIONS:** mtDNA haplogroups were associated with IR and atherogenic dyslipidemia; suggesting that mitochondrial genomics may play a significant role in metabolic disorders and cardiovascular diseases in HIV/hepatitis C virus-coinfected patients on highly active antiretroviral therapy.

Recent Hepatitis C Virus Infection in HIV-Infected Patients in Taiwan: Incidence and Risk Factors. Sun HY, Chang SY, Yang ZY, et al. J Clin Microbiol. 2011 Dec 21. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22189113>

Outbreaks of sexually transmitted hepatitis C virus (HCV) infections have been recently reported in HIV-infected men who have sex with men (MSM) in Europe, Australia, and North America. Little is known whether this also occurs in other Asia-Pacific countries. Between 1994 and 2010, a prospective observational cohort study was performed to assess the incidence of recent HCV seroconversion in 892 HIV-infected patients (731 MSM and 161 heterosexuals), who were not injecting drug users. A nested case-control study was conducted to identify associated factors with recent HCV seroconversion and phylogenetic analysis was performed using NS5B sequences amplified from seroconverters. During a total follow-up duration of 4270 person-years (PY), 30 patients (3.36%) had HCV seroconversion with an overall incidence rate of 7.03 per 1000 PY. The rate increased from 0 in 1994-2000, 2.29 in 2001-2005 to 10.13 per 1000 PY in 2006-2010 ($P < 0.05$). After adjustment for age and HIV transmission routes, recent syphilis remained an independent associated factor with HCV seroconversion (odds ratio, 7.731; 95% confidence interval, 3.131-19.086; $P < 0.01$). In nested case-control study, seroconverters had higher aminotransferase levels and were more likely to have $CD4 \geq 200$ cells/ μ L and recent syphilis than non-seroconverters ($P < 0.05$). Among the 21 patients with HCV viraemia, phylogenetic analysis revealed 7 HCV transmission clusters or pairs: 4 within genotype 1b, 2 within genotype 2a, and 1 within genotype 3a. The incidence of HCV seroconversion that is associated with recent syphilis is increasing among HIV-infected patients in Taiwan.

Neurocognitive Effects of HIV, Hepatitis C, and Substance Use History. Devlin KN, Gongvatana A, Clark US, et al. J Int Neuropsychol Soc. 2012 Jan;18(1):68-78. Epub 2011 Dec 2. <http://www.ncbi.nlm.nih.gov/pubmed/22132928>

HIV-associated neurocognitive dysfunction persists in the highly active antiretroviral therapy (HAART) era and may be exacerbated by comorbidities, including substance use and hepatitis C virus (HCV) infection. However, the neurocognitive impact of HIV, HCV, and substance use in the HAART era is still not well understood. In the current study, 115 HIV-infected and 72 HIV-seronegative individuals with significant rates of lifetime substance dependence and HCV infection received comprehensive neuropsychological assessment. We examined the effects of HIV serostatus, HCV infection, and substance use history on neurocognitive functioning. We also examined relationships between HIV disease measures (current and nadir CD4, HIV RNA, duration of infection) and cognitive functioning. Approximately half of HIV-infected participants exhibited neurocognitive impairment. Detectable HIV RNA but not HIV serostatus was significantly associated with cognitive functioning. HCV was among the factors most consistently associated with poorer neurocognitive performance across domains, while substance use was less strongly associated with cognitive performance. The results suggest that neurocognitive impairment continues to occur in HIV-infected individuals in association with poor virologic control and comorbid conditions, particularly HCV coinfection.

Prediction of response to pegylated interferon plus ribavirin in HIV/ hepatitis C virus (HCV)-coinfected patients using HCV genotype, IL28B variations and HCV-RNA load.

Neukam K, Camacho A, López-Biedma A, et al. J Hepatol. 2011 Dec 12. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22173157>

BACKGROUND & AIMS: This study aimed to develop a predictive algorithm based on interleukin 28B (IL28B) genotype, hepatitis C virus (HCV) genotype and plasma HCV-RNA load, which accurately allows us defining the probability of response to pegylated interferon (Peg-IFN) plus ribavirin (RBV) therapy in HIV/HCV-coinfected patients. **METHODS:** 521 treatment-naive HIV-infected patients who initiated HCV therapy with Peg-IFN/RBV were analysed in an on-treatment basis. Patients were categorized in unlikely responders, uncertain responders and anticipated responders (<20%, 20%-60% and >60% probability to achieve SVR, respectively). **RESULTS:** HCV genotype, baseline HCV-RNA load and IL28B genotype were confirmed as independent predictors of SVR in a logistic regression analysis. A stepwise algorithm based on these three variables was created in 321 patients and evaluated in the remaining 200 patients. Unlikely responders included patients with genotype 1 or 4, HCV-RNA load ≥ 600000 IU/mL and rs12979860 non-CC (rate of SVR: 17.3%). Anticipated responders were those with HCV genotype 2-3, patients harboring HCV genotype 4 and IL28B CC, as well as those who simultaneously bore HCV genotype 1, HCV-RNA load <600000 IU/mL and IL28B CC (rate of SVR 74.1%, 77.8% and 64.4%, respectively). The area under the receiver operating characteristic curve of the model was 0.77 (0.733-0.814). **CONCLUSION:** The combined use of IL28B genotype, HCV genotype and HCV-RNA load enables to easily identify patients with a high and very low likelihood of SVR. HCV therapy could be deferred in the latter patients, until more effective options are available, at least if they do not show advanced liver fibrosis.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

The green tea polyphenol, epigallocatechin-3-gallate, inhibits hepatitis C virus entry. Ciesek

S, von Hahn T, Colpitts CC, et al. Hepatology. 2011 Dec;54(6):1947-55. doi: 10.1002/

hep.24610.

<http://www.ncbi.nlm.nih.gov/pubmed/21837753>

Hepatitis C virus (HCV) is a major cause of liver cirrhosis and hepatocellular carcinoma. Current antiviral therapy fails to clear infection in a substantial proportion of cases. Drug development is focused on nonstructural proteins required for RNA replication. Individuals undergoing orthotopic liver transplantation face rapid, universal reinfection of the graft. Therefore, antiviral strategies targeting the early stages of infection are urgently needed for the prevention of HCV infection. In this study, we identified the polyphenol, epigallocatechin-3-gallate (EGCG), as an inhibitor of HCV entry. Green tea catechins, such as EGCG and its derivatives, epigallocatechin (EGC), epicatechin gallate (ECG), and epicatechin (EC), have been previously found to exert antiviral and antioncogenic properties. EGCG had no effect on HCV RNA replication, assembly, or release of progeny virions. However, it potently inhibited Cell-culture-derived HCV (HCVcc) entry into hepatoma cell lines as well as primary human hepatocytes. The effect was independent of the HCV genotype, and both infection of cells by extracellular virions and cell-to-cell spread were blocked. Pretreatment of cells with EGCG before HCV inoculation did not reduce HCV infection, whereas the application of EGCG during inoculation strongly inhibited HCV infectivity. Moreover, treatment with EGCG directly during inoculation strongly inhibited HCV infectivity. Expression levels of all known HCV (co-)receptors were unaltered by EGCG.

Finally, we showed that EGCG inhibits viral attachment to the cell, thus disrupting the initial step of HCV cell entry. **CONCLUSION:** The green tea molecule, EGCG, potently inhibits HCV entry and could be part of an antiviral strategy aimed at the prevention of HCV reinfection after liver transplantation.

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

HCV core antigen testing in HIV- and HBV-coinfected patients, and in HCV-infected patients on hemodialysis. Mederacke I, Potthoff A, Meyer-Olson D, et al. J Clin Virol. 2011 Dec 14. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22177274>

BACKGROUND: A quantitative HCV core antigen (HCVcoreAg) immunoassay has been developed for the confirmation of viremia in patients with hepatitis C. **OBJECTIVES:** We evaluated the correlation of HCV RNA and HCVcoreAg in different patient populations without HCV-specific treatment: HIV/HCV-coinfection, HBV/HCV-coinfection, and patients with end-stage renal disease. **STUDY DESIGN:** HCVcoreAg was quantified by a fully-automated immunoassay. Correlation of HCVcoreAg with HCV RNA was studied cross-sectionally in HIV/HCV- and HBV/HCV-coinfected patients, as well as before and after hemodialysis in patients with end-stage renal disease. **RESULTS:** A concordant positive or negative test result for both HCV RNA and HCVcoreAg was observed in 68 of 71 (96%), 55 of 57 (96%), and in 109 of 109 (100%) samples of patients with HIV- or HBV/HCV-coinfection, and patients undergoing hemodialysis, respectively. HCVcoreAg showed high correlation with HCV RNA in samples from HIV/HCV-coinfected patients and HCV-infected patients undergoing hemodialysis ($r=0.97$ and $r=0.94$, $p<0.001$). There was no overall correlation between HCVcoreAg and HCV RNA in HBV/HCV-coinfected individuals ($r=0.04$, $p=0.822$). Excluding patients with HCV RNA to HCVcoreAg ratios below 100 and above 10,000kIU/fmol led to improved correlation ($r=0.53$; $p=0.02$), but remained worse than for the other cohorts. Overall, HCV RNA to HCVcoreAg ratios did not differ significantly between the different patient populations, though variation tended to be higher in HBV/HCV-coinfected patients. Patients with lower HCV RNA levels tend to have lower HCV RNA/HCVcoreAg ratios. **CONCLUSIONS:** HCVcoreAg represents a reliable marker of viral replication showing a good correlation with HCV RNA in various patient populations, with some limitations in HBV/HCV-coinfection.

Cost-effectiveness of hepatitis C virus antiviral treatment for injection drug user populations. Martin NK, Vickerman P, Miners A, Foster GR, Hutchinson SJ, Goldberg DJ, Hickman M. Hepatology. 2012 Jan;55(1):49-57. doi: 10.1002/hep.24656. Epub 2011 Dec 6. <http://www.ncbi.nlm.nih.gov/pubmed/21898506>

Injecting drug use is the main risk of hepatitis C virus (HCV) transmission in most developed countries. HCV antiviral treatment (peginterferon- α + ribavirin) has been shown to be cost-effective for patients with no reinfection risk. We examined the cost-effectiveness of providing antiviral treatment for injecting drug users (IDUs) as compared with treating ex/non-IDUs or no treatment. A dynamic model of HCV transmission and disease progression was developed, incorporating: a fixed number of antiviral treatments allocated at the mild HCV stage over 10 years, no retreatment after treatment failure, potential reinfection, and three baseline IDU HCV chronic prevalence scenarios (20%, 40%, and 60%). We performed a probabilistic cost-utility

analysis estimating long-term costs and outcomes measured in quality adjusted life years (QALYs) and calculating the incremental cost-effectiveness ratio (ICER) comparing treating IDUs, ex/non-IDUs, or no treatment. Antiviral treatment for IDUs is the most cost-effective option in the 20% and 40% baseline chronic prevalence settings, with ICERs compared with no treatment of £521 and £2,539 per QALY saved, respectively. Treatment of ex/non-IDUs is dominated in these scenarios. At 60% baseline prevalence, treating ex/non-IDUs is slightly more likely to be the more cost-effective option (with an ICER compared with no treatment of £6,803), and treating IDUs dominated due to high reinfection. A sensitivity analysis indicates these rankings hold even when IDU sustained viral response rates as compared with ex/non-IDUs are halved. **CONCLUSION:** Despite the possibility of reinfection, the model suggests providing antiviral treatment to IDUs is the most cost-effective policy option in chronic prevalence scenarios less than 60%. Further research on how HCV treatment for injectors can be scaled up and its impact on prevalence is warranted.

Interventions to prevent sexually transmitted infections, including HIV infection. Marrazzo JM, Cates W. Clin Infect Dis. 2011 Dec;53 Suppl 3:S64-78.

<http://www.ncbi.nlm.nih.gov/pubmed/22080271>

The Centers for Disease Control and Prevention (CDC) Sexually Transmitted Disease (STD) Treatment Guidelines were last updated in 2006. To update the "Clinical Guide to Prevention Services" section of the 2010 CDC STD Treatment Guidelines, we reviewed the recent science with reference to interventions designed to prevent acquisition of STDs, including human immunodeficiency virus (HIV) infection. Major interval developments include (1) licensure and uptake of immunization against genital human papillomavirus, (2) validation of male circumcision as a potent prevention tool against acquisition of HIV and some other sexually transmitted infections (STIs), (3) failure of a promising HIV vaccine candidate to afford protection against HIV acquisition, (4) encouragement about the use of antiretroviral agents as preexposure prophylaxis to reduce risk of HIV and herpes simplex virus acquisition, (5) enhanced emphasis on expedited partner management and rescreening for persons infected with Chlamydia trachomatis and Neisseria gonorrhoeae, (6) recognition that behavioral interventions will be needed to address a new trend of sexually transmitted hepatitis C among men who have sex with men, and (7) the availability of a modified female condom. A range of preventive interventions is needed to reduce the risks of acquiring STI, including HIV infection, among sexually active people, and a flexible approach targeted to specific populations should integrate combinations of biomedical, behavioral, and structural interventions. These would ideally involve an array of prevention contexts, including (1) communications and practices among sexual partners, (2) transactions between individual clients and their healthcare providers, and (3) comprehensive population-level strategies for prioritizing prevention research, ensuring accurate outcome assessment, and formulating health policy.

Help-seeking and coping with the psychosocial burden of chronic hepatitis C: A qualitative study of patient, hepatologist, and counsellor perspectives. Stewart BJ, Mikocka-Walus AA, Harley H, Andrews JM. Int J Nurs Stud. 2011 Dec 6. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22154094>

BACKGROUND: Chronic hepatitis C affects millions of people worldwide, may have significant physical consequences, and patients are also at increased risk of psychiatric morbidity. However, it is currently unknown how patients cope with, and seek help for the

psychosocial issues which contribute to this psychiatric morbidity. **OBJECTIVES:** This study aimed to qualitatively explore the biopsychosocial burden of chronic hepatitis C, patients' subsequent coping and help-seeking, and the patient-health professional relationship from the different perspectives of patients, hepatologists, and counsellors. **METHODS:** Thirteen patients, five hepatologists, and two hepatitis C specific counsellors from South Australia participated in semi-structured interviews, which were audio-recorded, transcribed verbatim, and analysed thematically. **RESULTS:** All groups perceived chronic hepatitis C as a severe disease involving inextricably intertwined biological, psychological, and social impacts. Negative factors included the impact of diagnosis, stigmatisation, and often unwarranted fears regarding transmission and disease progression. The key positive influences reported across the groups involved information provision and access to informal and formal support. However, a number of barriers were noted to accessing this support, particularly stigmatisation. All respondents highlighted the importance of the patient-health professional relationship. This relationship was perceived to be enhanced by empathetic, compassionate professionals who provided comprehensive information in a sensitive and timely manner. Key negative influences on this relationship included discrimination or inappropriate treatment from mainstream health professionals, time constraints of doctors, patient non-attendance, and discordant views regarding treatment decisions. **CONCLUSIONS:** Reducing the psychosocial impact of chronic hepatitis C requires targeted information provision for patients, the general public, and mainstream health services. This may increase patient education, reduce the extent and impact of stigmatisation, remove barriers to help-seeking, and improve the patient-health professional relationship.

LIVER CANCER

Tumor necrosis factor-alpha -308G/A polymorphism and risk of hepatocellular carcinoma in hepatitis C virus-infected patients. Talaat RM, Esmail AA, Elwakil R, Gurgis AA, Nasr MI. *Chin J Cancer*. 2011 Dec 23. doi: 10.5732/cjc.011.10258. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22200181>

Tumor necrosis factor-alpha (TNF- α) is an important cytokine in generating an immune response against infection with hepatitis C virus (HCV). The functions of TNF- α may be altered by single-nucleotide polymorphisms (SNPs) in its gene structure. We hypothesized that SNPs in TNF- α may be important in determining the outcome of an HCV infection. To test this hypothesis, we investigated the role of the polymorphism -308G/A, which is located in the promoter region of the TNF- α gene, in the progression of HCV infection in Egyptian patients using a quantitative real-time polymerase chain reaction (qRT-PCR). The distribution of this polymorphism and its impact on the serum level of TNF- α was compared between 90 HCV-infected patients [45 with HCV-induced cirrhosis and 45 with HCV-related hepatocellular carcinoma (HCC)] and 45 healthy Egyptian volunteers without any history of liver disease. Our results showed that at the TNF- α -308 position, the G/G allele was most common (78.5%) in the study population, with the G/A and A/A alleles occurring less frequently (13.3% and 8.1%, respectively). Frequencies of G/G, G/A, and A/A genotypes was 87%, 7%, and 6% in patients with liver cirrhosis and were 94%, 4%, and 2% in patients with HCC, respectively. Serum levels of TNF- α were significantly higher in HCV-infected patients than in healthy controls, indicating that the TNF- α -308 polymorphism does not influence the production of TNF- α . The serum level of TNF- α was positively correlated with HCV infection. Taken together, these findings suggest that the TNF- α -

308 polymorphism may not be a host genetic factor associated with the severity of HCV infection, but may be an independent risk factor for HCC.

Recent Trends of Japanese Hepatocellular Carcinoma due to HCV in Aging Society.

Hiraoka A, Hidaka S, Shimizu Y, et al. Hepatogastroenterology. 2011 Dec 22;59(118). doi: 10.5754/hge11732. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22193439>

BACKGROUND/AIMS: The mean age of hepatocellular carcinoma (HCC) patients has increased (=65 years old). We want to identify the recent trend of the clinical features of HCC patients due to hepatitis C virus (HCV) (HCV-HCC). **METHODOLOGY:** From 2000 to 2009, 855 naive HCC patients were admitted. HCV-HCC patients were divided into two groups, first period group (2000-04, n=270) and second period group (2005-09, n=343) and the clinical features of HCV-HCC were investigated. **RESULTS:** There was no difference in gender, TNM stage and percentages of HCV-HCC between the periods. On the other hand, the ratio of HCV-HCC patients with worse liver function (Child-Pugh B or C), elderly (=75 years old) and the population of patients treated with low invasive radiofrequency ablation were increased (30.0% to 42.0%, 17.2% to 35.8% and 25.1% to 36.2%, respectively; $p<0.01$). The 1y-, 3y- and 5y-survival rate of HCV-HCC did not show differences (82.1%, 60.5% and 44.7% vs. 81.8%, 56.9% and 37.7%, respectively; $p=0.219$). **CONCLUSIONS:** The ratio of aged HCV-HCC as well as HCV-HCC patients with worse liver function was increased. The less invasive treatment for HCC in these patients and the quick anti-viral treatment for HCV patients should be considered to avoid occurrence of HCC in Japan.

Outcomes of curative treatment for hepatocellular cancer in nonalcoholic steatohepatitis versus hepatitis C and alcoholic liver disease. Reddy SK, Steel JL, Chen HW, et al.

Hepatology. 2011 Dec 20. doi: 10.1002/hep.25536. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22183968>

BACKGROUND AND AIMS: Concomitant increasing incidences of hepatocellular carcinoma (HCC) and nonalcoholic steatohepatitis (NASH) suggests that a substantial proportion of HCC arises due to hepatocellular injury from NASH. The objective of this study is to determine differences in severity of liver dysfunction at HCC diagnosis and long-term survival outcomes between patients undergoing curative therapy for HCC in the background of NASH compared to hepatitis C virus (HCV) and/or alcoholic liver disease. **METHODS:** Patient demographics and comorbidities, clinicopathologic data, and long-term outcomes among patients who underwent liver transplantation, hepatic resection, or radiofrequency ablation for HCC were reviewed. **RESULTS:** From 2000-2010, 303 patients underwent curative treatment of HCC; 52 (17.2%) and 162 (53.5%) had NASH and HCV and/or alcoholic liver disease. At HCC diagnosis, NASH patients were older (median 65 vs. 58 years), more often female (48.1% vs. 16.7%), more often had the metabolic syndrome (45.1% vs. 14.8%), and had lower model for end-stage liver disease scores (median 9 vs. 10), all $p<0.05$. NASH patients were less likely to have hepatic bridging fibrosis or cirrhosis (73.1% vs. 93.8%, $p<0.001$). After a median follow-up of 50 months after curative treatment, the most frequent cause of death was liver failure. While there were no difference in recurrence free survival after curative therapy (median 60 vs. 56 months, $p=0.303$), NASH patients had longer overall survival (median not reached vs. 52 months, $p=0.009$) independent of other clinicopathologic factors and type of curative treatment. **CONCLUSIONS:**

Patients with HCC in the setting of NASH have less severe liver dysfunction at HCC diagnosis and better overall survival after curative treatment compared to counterparts with HCV and/or alcoholic liver disease.

Difference in malignancies of chronic liver disease due to non-alcoholic fatty liver disease or hepatitis C in Japanese elderly patients. Arase Y, Kobayashi M, Suzuki F, et al. *Hepatol Res.* 2011 Dec 19. doi: 10.1111/j.1872-034X.2011.00915.x. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/22175908>

AIM: Malignancies that include hepatocellular carcinoma often occurred in patients with chronic liver disease. The aim of this retrospective match control study was to assess the cumulative development incidence and predictive factors for total malignancies in elderly Japanese patients with non-alcoholic hepatic diseases (NAFLD) or hepatitis C virus (HCV). **METHODS:** A total of 1600 NAFLD patients with age of ≥ 60 years were enrolled, and 1600 HCV patients with age of ≥ 60 years were selected as control by matching 1:1 with NAFLD group for age, sex, and follow-up period. The primary goal is the first development of malignancies. Evaluation was performed by the use of the Wilcoxon rank sum test, the Kaplan-Meier method, and Cox proportional hazard model. The mean observation period is 8.2 years in both NAFLD and HCV group, respectively. **RESULTS:** The number of patients with the development of malignancies was 167 in the NAFLD group and 395 in the HCV group. The 10th development rate of malignancies was 13.9% in the NAFLD group and 28.2% in the HCV group (risk ratio 2.27; $P < 0.001$). The incident rates of hepatocellular carcinoma in all the malignancies were 6.0% (10/167) in the NAFLD group and 67.6% (267/395) in the HCV group ($P < 0.001$). The malignancies in the NAFLD group were observed in the following order: gastric cancer 34 cases (20.4%) > colon cancer 31 cases (18.6%) > prostate cancer 21 cases (12.6%). **Conclusions:** The incident rates of hepatocellular carcinoma in all the malignancies were approximately 6% in the NAFLD group and two-thirds in the HCV group.

Hepatic arterial infusion chemotherapy using 5-fluorouracil and systemic interferon- α for advanced hepatocellular carcinoma in combination with or without three-dimensional conformal radiotherapy to venous tumor thrombosis in hepatic vein or inferior vena cava. Murakami E, Aikata H, Miyaki D, et al. *Hepatol Res.* 2011 Dec 16. doi: 10.1111/j.1872-034X.2011.00943.x. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/22176468>

Aim: We investigated the efficacy of hepatic arterial infusion chemotherapy (HAIC) using 5-fluorouracil (5-FU) and systemic interferon (IFN)- α (HAIC-5-FU/IFN) for advanced hepatocellular carcinoma (HCC) with venous tumor thrombosis (VTT) in the hepatic vein trunk (Vv2) or inferior vena cava (Vv3). **METHODS:** Thirty-three patients with HCC/Vv2/3 underwent HAIC with 5-FU (500 mg/body weight/day, into hepatic artery on days 1-5 on the first and second weeks) and IFN- α (recombinant IFN- α -2b 3 000 000 U or natural IFN- α 5 000 000 U, intramuscularly on days 1, 3 and 5 of each week). Three-dimensional conformal radiotherapy (3D-CRT) was used in combination with HAIC-5-FU/IFN in 14 of 33 patients to reduce VTT. **RESULT:** The median survival time (MST) was 7.9 months, and 1- and 2-year survival rates were 30% and 20%, respectively. Evaluation of intrahepatic response after two cycles of HAIC-5-FU/IFN showed complete response (CR) in three (9%) and partial response (PR) in seven (21%), with an objective response rate of 30%. Multivariate analysis identified reduction of VTT ($P = 0.0006$), size of largest tumor ($P = 0.013$) and intrahepatic response

CR/PR (P = 0.030) as determinants of survival. CR/PR correlated significantly with tumor liver occupying rate (P = 0.016) and hepatitis C virus Ab (P = 0.010). Reduction of VTT correlated significantly with radiotherapy (P = 0.021) and platelet count (P = 0.015). Radiotherapy-related reduction in VTT significantly improved survival of 16 patients with Vv3 and non-CR/PR response of HAIC-5-FU/IFN (P = 0.028). **CONCLUSION:** As for advanced HCC with VTT of Vv2/3, HAIC-5-FU/IFN responsive patients could obtain favorable survival. Despite ineffective HAIC-5-FU/IFN, the combination with effective radiotherapy to VTT might improve patients' prognosis.

A dual role for hypoxia inducible factor-1 α in the hepatitis C virus lifecycle and hepatoma migration. Wilson GK, Brimacombe CL, Rowe IA, et al. J Hepatol. 2011 Dec 15. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22178269>

BACKGROUND AND AIMS: Hepatitis C virus (HCV) causes progressive liver disease and is a major risk factor for the development of hepatocellular carcinoma (HCC). However, the role of infection in HCC pathogenesis is poorly understood. We investigated the effect(s) of HCV infection and viral glycoprotein expression on hepatoma biology to gain insights into the development of HCV associated HCC. **METHODS:** We assessed the effect(s) of HCV and viral glycoprotein expression on hepatoma polarity, migration and invasion. **RESULTS:** HCV glycoproteins perturb tight and adherens junction protein expression, increase hepatoma migration and expression of epithelial to mesenchymal transition markers Snail and Twist via stabilizing hypoxia inducible factor-1 α (HIF-1 α). HIF-1 α regulates many genes involved in tumor growth and metastasis, including vascular endothelial growth factor (VEGF) and transforming growth factor-beta (TGF- β). Neutralization of growth factors show different roles for VEGF and TGF- β in regulating hepatoma polarity and migration, respectively. Importantly, we confirmed these observations in virus infected hepatoma and primary human hepatocytes. Inhibition of HIF-1 α reversed the effect(s) of infection and glycoprotein expression on hepatoma permeability and migration and significantly reduced HCV replication, demonstrating a dual role for HIF-1 α in the cellular processes that are deregulated in many human cancers and in the viral life cycle. **CONCLUSIONS:** These data provide new insights into the cancer-promoting effects of HCV infection on HCC migration and offer new approaches for treatment.

Radiofrequency Ablation for Hepatocellular Carcinoma: 10-Year Outcome and Prognostic Factors. Shiina S, Tateishi R, Arano T, et al. Am J Gastroenterol. 2011 Dec 13. doi: 10.1038/ajg.2011.425. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22158026>

OBJECTIVES: Radiofrequency ablation (RFA) is widely performed for hepatocellular carcinoma (HCC). However, there has been no report on 10-year outcome of RFA. The objective of this study was to report a 10-year consecutive case series at a tertiary referral center. **METHODS:** We performed 2,982 RFA treatments on 1,170 primary HCC patients and analyzed a collected database. **RESULTS:** Final computed tomography images showed complete tumor ablation in 2,964 (99.4%) of 2,982 treatments performed for the 1,170 primary HCC patients. With a median follow-up of 38.2 months, 5- and 10-year survival rates were 60.2% (95% confidence interval (CI): 56.7-63.9%) and 27.3% (95% CI: 21.5-34.7%), respectively. Multivariate analysis demonstrated that age, antibody to hepatitis C virus (anti-HCV), Child-Pugh class, tumor size, tumor number, serum des- γ -carboxy-prothrombin (DCP) level, and

serum lectin-reactive α -fetoprotein level (AFP-L3) were significantly related to survival. Five- and 10-year local tumor progression rates were both 3.2% (95% CI: 2.1-4.3%). Serum DCP level alone was significantly related to local tumor progression. Five- and 10-year distant recurrence rates were 74.8% (95% CI: 71.8-77.8%) and 80.8% (95% CI: 77.4-84.3%), respectively. Anti-HCV, Child-Pugh class, platelet count, tumor size, tumor number, serum AFP level, and serum DCP level were significantly related to distant recurrence. There were 67 complications (2.2%) and 1 death (0.03%). **CONCLUSIONS:** RFA could be locally curative for HCC, resulting in survival for as long as 10 years, and was a safe procedure. RFA might be a first-line treatment for selected patients with early-stage HCC.

Recent trend of clinical features in patients with hepatocellular carcinoma. Nagaoki Y, Hyogo H, Aikata H, et al. *Hepatol Res.* 2011 Dec 13. doi: 10.1111/j.1872-034X.2011.00929.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/22151896>

AIM: In this study, we evaluated the clinical characteristics of hepatocellular carcinoma (HCC) because the etiology of HCC has been changing recently. **METHODS:** Consecutive 1374 HCC patients at our institution from 1995 to 2009 were enrolled and clinical characteristics were investigated. **RESULTS:** Seventeen percent and 67% of HCC were related to hepatitis B virus (HBV-HCC) and hepatitis C virus (HCV-HCC), respectively. Fifteen percent of that was negative for hepatitis B surface antigen (HBsAg) and antibody to hepatitis C virus (HCVAb) (NBNC-HCC). HCV-HCC tended to decrease and NBNC-HCC tended to increase in recent years. Patients with NBNC-HCC and HCV-HCC were significantly older than those with HBV-HCC. The complication rates of diabetes mellitus (DM), heavy alcohol consumption, hypertension, and hyperlipidemia in NBNC-HCC were significantly higher than those in other groups. Furthermore, the platelet counts and body mass index in NBNC-HCC were significantly higher than those of other groups. Among 209 NBNC-HCC patients, 58 patients underwent hepatic resection in which 29%, 36%, and 35% of those were based on non-alcoholic steatohepatitis (NASH), heavy alcohol consumption, and unknown etiology, respectively. DM was prevalent especially in NASH and heavy alcohol consumption. Cirrhosis was detected in 65%, 81%, and 15% in NASH-HCC, heavy alcohol consumption-HCC, and unknown etiology, respectively. **CONCLUSIONS:** NBNC-HCC has gradually been increasing in recent years. The present study elucidated that the presence of NASH and metabolic syndrome were important risk factors for NBNC-HCC and suggests that these patients should receive surveillance for HCC development.

Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis: A randomized trial comparing 3- and 6-month periodicities. Trinchet JC, Chaffaut C, Bourcier V, Degos F, et al. *Hepatology.* 2011 Dec;54(6):1987-1997. doi: 10.1002/hep.24545.

<http://www.ncbi.nlm.nih.gov/pubmed/22144108>

Detection of small hepatocellular carcinoma (HCC) eligible for curative treatment is increased by surveillance, but its optimal periodicity is still debated. Thus, this randomized trial compared two ultrasonographic (US) periodicities: 3 months versus 6 months. A multicenter randomized trial was conducted in France and Belgium (43 sites). Patients with histologically proven compensated cirrhosis were randomized into two groups: US every 6 months (Gr6M) or 3 months (Gr3M). For each focal lesion detected, diagnostic procedures were performed according to European Association for the Study of the Liver guidelines. Cumulative incidence of events

was estimated, then compared using Gray's test. The prevalence of HCC ≤ 30 mm in diameter was the main endpoint. A sample size of 1,200 patients was required. A total of 1,278 patients were randomized (Gr3M, n = 640; Gr6M, n = 638; alcohol 39.2%, hepatitis C virus 44.1%, hepatitis B virus 12.5%). At least one focal lesion was detected in 358 patients (28%) but HCC was confirmed in only 123 (9.6%) (uninodular 58.5%, ≤ 30 mm in diameter 74%). Focal-lesion incidence was not different between Gr3M and Gr6M groups (2-year estimates, 20.4% versus 13.2%, $P = 0.067$) but incidence of lesions ≤ 10 mm was increased (41% in Gr3M versus 28% in Gr6M, $P = 0.002$). No difference in either HCC incidence ($P = 0.13$) or in prevalence of tumors ≤ 30 mm in diameter (79% versus 70%, $P = 0.30$) was observed between the randomized groups. **CONCLUSION:** US surveillance, performed every 3 months, detects more small focal lesions than US every 6 months, but does not improve detection of small HCC, probably because of limitations in recall procedures.

Risk factors for hepatocellular carcinoma in a cohort infected with hepatitis B or C.

Walter SR, Thein HH, Gidding HF, Amin J, Law MG, George J, Dore GJ. *J Gastroenterol Hepatol.* 2011 Dec;26(12):1757-64. doi: 10.1111/j.1440-1746.2011.06785.x.

<http://www.ncbi.nlm.nih.gov/pubmed/21615789>

BACKGROUND AND AIM: The incidence of hepatocellular carcinoma (HCC) has increased in Australia in recent decades, a large and growing proportion of which occurs among a population chronically infected with hepatitis B virus (HBV) or hepatitis C virus (HCV). However, risk factors for HCC among these high-risk groups require further characterization.

METHODS: We conducted a population-based cohort study using HBV and HCV cases notified to the New South Wales Health Department between 2000 and 2007. These were linked to cause of death data, HIV/AIDS notifications, and hospital records. Proportional hazards regression was used to identify significant risk factors for developing HCC. **RESULTS:**

A total of 242 and 339 HCC cases were linked to HBV (n = 43 892) and HCV (n = 83 817) notifications, respectively. For both HBV and HCV groups, being male and increasing age were significantly associated with risk of HCC. Increasing comorbidity score indicated high risk, while living outside urban areas was associated with lower risk. Hazard ratios for males were two to three times those of females. For both HBV and HCV groups, cirrhosis, alcoholic liver disease, and the interaction between the two were associated with significantly and considerably elevated risk. **CONCLUSION:** This large population-based study confirms known risk factors for HCC. The association with older age highlights the potential impact of HBV and HCV screening of at-risk groups and early clinical assessment. Additional research is required to evaluate the impact of improving antiviral therapy on HCC risk.

Pyogenic liver abscess as the initial manifestation of underlying hepatocellular carcinoma.

Lin YT, Liu CJ, Chen TJ, et al. *Am J Med.* 2011 Dec;124(12):1158-64.

<http://www.ncbi.nlm.nih.gov/pubmed/22114829>

BACKGROUND: Pyogenic liver abscess and hepatocellular carcinoma are common in Taiwan. We investigated the frequency of, risk factors for, and prognosis of pyogenic liver abscess as the initial manifestation of underlying hepatocellular carcinoma over a 12-year period in Taiwan.

METHODS: We extracted 32,454 patients with pyogenic liver abscess from a nationwide health registry in Taiwan during the period 1997-2008. The frequency of and risk factors for pyogenic liver abscess as the initial manifestation of underlying hepatocellular carcinoma were determined. The prognosis of these patients was compared with patients with hepatocellular

carcinoma but without liver abscess. **RESULTS:** A total of 698 (2.15%) patients presented with liver abscess as the initial manifestation of underlying hepatocellular carcinoma during the 12-year period. Liver cirrhosis, hepatitis B virus infection, hepatitis C virus infection, and age ≥ 65 years were independent risk factors for liver abscess as the initial manifestation of underlying hepatocellular carcinoma. Furthermore, these patients had a lower 2-year survival rate than patients with hepatocellular carcinoma but without liver abscess (30% vs 37%; $P=.004$).

CONCLUSIONS: The prognosis of patients who presented with pyogenic liver abscess as the initial manifestation of underlying hepatocellular carcinoma was poor. Physicians should not ignore the possibility of underlying hepatocellular carcinoma in patients with risk factors for the disease in regions with a high prevalence of both pyogenic liver abscess and hepatocellular carcinoma.