



# Caring Ambassadors Program Hepatitis C Newsletter

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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES	1 - 11
BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES	11 - 14
HIV/HCV/HBV COINFECTION	14 - 18
EPIDEMIOLOGY, DIAGNOSTICS & MISCELLANEOUS WORKS	19 - 22
LIVER CANCER	22 - 25

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## CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

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**Outcomes of treatment for hepatitis C virus infection by primary care providers.** Arora S, Thornton K, Murata G, et al. *N Engl J Med.* 2011 Jun 9;364(23):2199-207. Epub 2011 Jun 1.

<http://www.ncbi.nlm.nih.gov/pubmed/21631316>

**BACKGROUND:** The Extension for Community Healthcare Outcomes (ECHO) model was developed to improve access to care for underserved populations with complex health problems such as hepatitis C virus (HCV) infection. With the use of video-conferencing technology, the ECHO program trains primary care providers to treat complex diseases. **METHODS:** We conducted a prospective cohort study comparing treatment for HCV infection at the University of New Mexico (UNM) HCV clinic with treatment by primary care clinicians at 21 ECHO sites in rural areas and prisons in New Mexico. A total of 407 patients with chronic HCV infection who had received no previous treatment for the infection were enrolled. The primary end point was a sustained virologic response. **RESULTS:** A total of 57.5% of the patients treated at the UNM HCV clinic (84 of 146 patients) and 58.2% of those treated at ECHO sites (152 of 261 patients) had a sustained viral response (difference in rates between sites, 0.7 percentage points; 95% confidence interval, -9.2 to 10.7;  $P=0.89$ ). Among patients with HCV genotype 1 infection, the rate of sustained viral response was 45.8% (38 of 83 patients) at the UNM HCV clinic and 49.7% (73 of 147 patients) at ECHO sites ( $P=0.57$ ). Serious adverse events occurred in 13.7% of the patients at the UNM HCV clinic and in 6.9% of the patients at ECHO sites.

**CONCLUSIONS:** The results of this study show that the ECHO model is an effective way to treat HCV infection in underserved communities. Implementation of this model would allow other states and nations to treat a greater number of patients infected with HCV than they are currently able to treat.

**Genetic variation in interleukin 28B with respect to vertical transmission of hepatitis C virus and spontaneous clearance in HCV-infected children.** Ruiz-Extremera A, Muñoz-Gómez JA, Salmerón-Ruiz MA, et al. *Hepatology.* 2011 Jun;53(6):1830-8. doi:

10.1002/hep.24298.

<http://www.ncbi.nlm.nih.gov/pubmed/21413051>

The vertical transmission of hepatitis C virus (HCV-VT) is a major route of HCV infection in children, but the risk factors remain incompletely understood. This study analyzed the role of interleukin 28B (IL28B) in HCV-VT and in the spontaneous clearance of HCV among infected infants. Between 1991 and 2009, 145 mothers were recruited for this study: 100 were HCV-

RNA+ve / human immunodeficiency virus negative (HIV-ve), with 128 children, and 33 were HCV-RNA-ve/HCV antibody+ve, with 43 children. The infants were tested for HCV-RNA at birth and at regular intervals until the age of 6 years. IL28B (single nucleotide polymorphism rs12979860) was determined in the mothers and children. HCV-VT was assumed when children presented HCV-RNA+ve in two subsequent blood samples. HCV-VT-infected infants were categorized as: (1) transient viremia with posterior HCV-RNA-ve and without serum-conversion; (2) persistent infection with serum-conversion. Of the 31 mothers with CC polymorphism, 19 (61%) were HCV-RNA+ve, whereas among the 68 mothers with non-CC polymorphism, 56 (82%) were HCV-RNA+ve. In all, 26 of 128 (20%) infants born to the HCV-RNA+ve mothers acquired HCV infection, but only 9 (7%) were chronically infected. The rate of HCV-VT was higher among the mothers with higher HCV viremia. No HCV-VT was detected in the HCV-RNA-ve women. Neither the mothers' nor the childrens' IL-28 status was associated with an increased risk of HCV-VT. The factors influencing viral clearance among the infected children were genotype non-1 and genotype CC of IL28B. In logistic regression, child CC polymorphism was the only predictor of HCV-clearance in HCV genotype-1. **CONCLUSION:** High maternal viral load is the only predictive factor of HCV-VT. IL28B plays no role in HCV-VT, but IL28B CC child polymorphism is associated independently with the spontaneous clearance of HCV genotype-1 among infected children.

**Telaprevir for retreatment of HCV infection.** Zeuzem S, Andreone P, Pol S, et al. N Engl J Med. 2011 Jun 23;364(25):2417-28.

<http://www.ncbi.nlm.nih.gov/pubmed/21696308>

**BACKGROUND:** Up to 60% of patients with hepatitis C virus (HCV) genotype 1 infection do not have a sustained virologic response to therapy with peginterferon alfa plus ribavirin.

**METHODS:** In this randomized, phase 3 trial, we evaluated the addition of telaprevir to peginterferon alfa-2a plus ribavirin in patients with HCV genotype 1 infection who had no response or a partial response to previous therapy or who had a relapse after an initial response. A total of 663 patients were assigned to one of three groups: the T12PR48 group, which received telaprevir for 12 weeks and peginterferon plus ribavirin for a total of 48 weeks; the lead-in T12PR48 group, which received 4 weeks of peginterferon plus ribavirin followed by 12 weeks of telaprevir and peginterferon plus ribavirin for a total of 48 weeks; and the control group (PR48), which received peginterferon plus ribavirin for 48 weeks. The primary end point was the rate of sustained virologic response, which was defined as undetectable HCV RNA 24 weeks after the last planned dose of a study drug. **RESULTS:** Rates of sustained virologic response were significantly higher in the two telaprevir groups than in the control group among patients who had a previous relapse (83% in the T12PR48 group, 88% in the lead-in T12PR48 group, and 24% in the PR48 group), a partial response (59%, 54%, and 15%, respectively), and no response (29%, 33%, and 5%, respectively) ( $P < 0.001$  for all comparisons). Grade 3 adverse events (mainly anemia, neutropenia, and leukopenia) were more frequent in the telaprevir groups than in the control group (37% vs. 22%). **CONCLUSIONS:** Telaprevir combined with peginterferon plus ribavirin significantly improved rates of sustained virologic response in patients with previously treated HCV infection, regardless of whether there was a lead-in phase.

**A Poxvirus Vaccine Is Safe, Induces T-Cell Responses, and Decreases Viral Load in Patients With Chronic Hepatitis C.** Habersetzer F, Honnet G, Bain C, et al. *Gastroenterology*. 2011 Jun 13. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21699798>

**BACKGROUND & AIMS:** Therapy for chronic hepatitis C (CHC) has limited efficacy, adverse effects, and high costs. Cohort and vaccine-based preclinical studies have indicated the importance of T-cell-based immunity in controlling viral infection. TG4040 is a recombinant poxvirus vaccine that expresses the HCV proteins NS3, NS4, and NS5B. We performed a phase I clinical trial to assess the safety, immunogenicity, and antiviral efficacy of TG4040 in patients with CHC. **METHODS:** In an open-label, dose-escalating study, patients with mild CHC (genotype 1) were assigned to 3 groups of 3 patients each; they received subcutaneous (SC) injections of 10(6), 10(7), or 10(8) plaque-forming units (PFU) of TG4040 on study days 1, 8, and 15. Six additional patients were given the highest dose of vaccine (10(8) PFU). Patients were followed for 6 months after the last injection. Immune responses, anti-HCV specific responses, and HCV RNA levels were measured. **RESULTS:** All 3 doses of TG4040 were well tolerated, without serious adverse events. Vaccine-induced HCV-specific cellular immune responses were observed in 5 of the 15 patients (33%). A transient decrease in circulating levels of HCV RNA, from -0.52 log(10) to -1.24 log(10), was observed in 8 patients; in 5 patients, the lowest level of HCV RNA was observed on day 37, after the first injection. The most pronounced decrease in viral load occurred in 2 patients, who also had marked vaccine-induced T-cell responses. **CONCLUSIONS:** A viral vector-based vaccine against HCV non-structural proteins is safe, can induce an anti-viral immune response, and reduce viral load in patients with CHC. TG4040 might be developed as a therapeutic agent for these patients.

**Rate of Progression of Hepatic Fibrosis in Patients with Chronic Hepatitis C: Results from the HALT-C Trial.** Hoefs JC, Shiffman ML, Goodman ZD, et al. *Gastroenterology*. 2011 Jun 12. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21699796>

**BACKGROUND & AIMS:** The gradual accumulation of hepatic fibrosis in chronic liver disease results in clinical complications. The rate of hepatic fibrosis score progression (RFSP) in predicting clinical outcomes was assessed by extending the 4-year HALT-C Trial to include preenrollment liver biopsies. **METHODS:** The RFSP was calculated from the linear regression slope of Ishak fibrosis score versus time in 457 patients with liver biopsies ( $\geq 10$  mm length) prior to the HALT-C Trial (575 biopsies) plus 1101 on-study biopsies (total 1676 biopsies). Individual slopes were calculated if duration from first to last biopsy was  $>4$  years. **RESULTS:** The RFSP as average fibrosis score versus average time in intervals (0-3 and  $>3$  years prestudy, screening, month 24 and 48 on-study) in 455 patients in cohorts of baseline Ishak score ranged from 0.005 with Ishak score 2 to 0.124 with Ishak 6. The RFSP in individual patients (-0.35 to +0.97 Ishak Units/year) had a mean of  $0.12 \pm 0.23$  in 344 patients with prestudy and onstudy biopsies (Group A) and  $0.17 \pm 0.22$  in 169 with prestudy and screening biopsies (Group B). Group A patients with RFSP slope  $\geq 0.2$ ; 95 patients; 27.6% had higher 7-year cumulative rates of non-HCC outcomes (46% versus 8%) and HCC (10% versus 3%) than RFSP slope  $< 0.2$ ; 249 patients, 72.4%) ( $P < 0.0001$ ). RFSP and screening Ishak score correlated independently ( $P < 0.0001$ ) with clinical outcomes in multivariate analysis. **CONCLUSIONS:** Rapid RFSP in 26.7 % of HALT-C Trial patients correlated strongly with clinical outcomes.

**Optimal follow-up time to determine the sustained virological response in patients with chronic hepatitis C receiving Peg-IFN and ribavirin.** Namikawa M, Kakizaki S, Yata Y, et al. *J Gastroenterol Hepatol.* 2011 Jun 7. doi: 10.1111/j.1440-1746.2011.06802.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21649727>

**BACKGROUND:** This study evaluated whether the assessment of HCV-RNA at 12 weeks (FW+12) post treatment follow-up was as applicable as FW+24 to evaluate sustained virological response (SVR) using the highly sensitive real-time PCR HCV assay. **METHODS AND**

**RESULTS:** Two hundred twenty-two patients with chronic hepatitis C were included in this study. Pegylated interferon (Peg-IFN) and ribavirin were administered for 24-72 weeks based on the genotype and viral load. Serum HCV-RNA was measured using real-time PCR at pretreatment, the end of treatment, FW + 4, FW + 8, FW + 12, FW + 16, FW+20 and FW+24. Two hundred patients had a virological response at the end of treatment. One hundred forty-eight of 200 (74.0%) patients with a virological response at the end of treatment had an SVR at the FW + 24. The positive predictive value (PPV) to identify patients with SVR at FW + 4, FW + 8, FW + 12 was 87.1, 96.1, 98.0%, respectively. The viral load showed a reversion to the basal level as early as 8 weeks in relapse patients. There were only 3 patients who relapsed after FW + 12 and all 3 of these patients were females with genotype 1b and a high viral load.

**CONCLUSION:** The assessment of serum HCV-RNA FW + 12, using the highly sensitive real-time PCR assay, is almost as effective as FW + 24 to predict SVR. However, there are false negatives in female patients with a high viral load of genotype 1b when the SVR is predicted by FW + 12. The current standard with FW + 24 is reasonable, but the assessment of serum HCV-RNA FW + 12 may be effective in most patients.

### **Prognostic factors in patients with hepatitis C virus infection and systemic vasculitis.**

Terrier B, Semoun O, Saadoun D, Sène D, Resche-Rigon M, Cacoub P. *Arthritis Rheum.* 2011 Jun;63(6):1748-57. doi: 10.1002/art.30319.

<http://www.ncbi.nlm.nih.gov/pubmed/21400476>

**OBJECTIVE:** Hepatitis C virus (HCV)-related systemic vasculitis can cause significant morbidity and mortality. Most studies of the prognosis of patients with HCV-related systemic vasculitis are based on heterogeneous studies performed before the era of antiviral therapy. The aim of this study was to analyze the clinical, biologic, and therapeutic factors associated with prognosis in a homogeneous series of patients with HCV-related systemic vasculitis who were followed up during the era of antiviral therapy. **METHODS:** One hundred fifty-one consecutive HCV RNA-positive patients with vasculitis were prospectively followed up between 1993 and 2009 and were analyzed for clinical, biologic, and therapeutic factors associated with survival. **RESULTS:** After a median followup period of 54 months, 32 patients (21%) had died, mainly of infection and end-stage liver disease. The 1-year, 3-year, 5-year, and 10-year survival rates were 96%, 86%, 75%, and 63%, respectively. Baseline factors associated with a poor prognosis were the presence of severe liver fibrosis (hazard ratio [HR] 5.31), central nervous system involvement (HR 2.74), kidney involvement (HR 1.91), and heart involvement (HR 4.2). The Five-Factors Score (FFS), a vasculitis scoring system, was significantly associated with outcome. In multivariate analysis, severe fibrosis (HR 10.8) and the FFS (HR 2.49) were significantly associated with a poor prognosis. Treatment with the combination of PEGylated interferon plus ribavirin was associated with a good prognosis (HR 0.34), whereas treatment with

immunosuppressive agents was associated with a poor outcome, after adjustment for the severity of vasculitis (HR 4.05). Among patients without severe fibrosis, the FFS was a good predictor of outcome, while among those with severe fibrosis, the severity of vasculitis had no prognostic value. **CONCLUSION:** At the time of the diagnosis of HCV-related systemic vasculitis, severe liver fibrosis and the severity of vasculitis were the main prognostic factors. Use of antiviral agents was associated with a good prognosis, whereas treatment with immunosuppressant agents had a negative impact.

**A prospective study of T- and B-lymphocyte subpopulations, CD81 expression levels on B cells and regulatory CD4(+) CD25(+) CD127(low/-) FoxP3(+) T cells in patients with chronic HCV infection during pegylated interferon-alpha2a plus ribavirin treatment.**

Soldevila B, Alonso N, Martínez-Arconada MJ, et al. J Viral Hepat. 2011 Jun;18(6):384-92. doi: 10.1111/j.1365-2893.2010.01317.x.

<http://www.ncbi.nlm.nih.gov/pubmed/20487258>

Resolution of hepatitis C virus (HCV) infection requires a complex interplay between innate and adaptative immune responses. The role of lymphocyte subpopulations during combined antiviral treatment remains to be defined. This study was conducted to assess the effect of pegylated interferon-alpha2a (pegIFN- $\alpha$ 2a) and ribavirin treatment on peripheral blood lymphocytes, mainly on CD81 expression on B cells and CD4(+) CD25(+) CD127(low/-) FoxP3(+) regulatory T cells (Tregs) in patients with chronic HCV infection. Thirty-five patients with chronic HCV infection who started pegIFN- $\alpha$ 2a and ribavirin treatment were enrolled. Peripheral blood mononuclear cells (PBMC) were obtained at baseline before treatment (BT), mid-treatment (MT), the end of treatment (ET) and 24weeks post-treatment (PT). During combined antiviral treatment, a significant decrease in the percentage of CD3(+) , CD8(+) , CD3(+) gamma/delta ( $\gamma\delta$ )(+) , CD19(+) lymphocyte subpopulations and Tregs was observed. There was also a significant increase in the percentage of the CD4(+) lymphocyte subpopulation and in CD81 expression levels on CD19(+) B cells when BT was compared with ET (all  $P < 0.05$ ). Seventeen patients were nonresponders (NR) and 18 had a sustained virological response (SVR). At baseline, NR patients had higher CD81 expression levels on CD19(+) B cells ( $P = 0.017$ ) and a higher Tregs percentage ( $P = 0.025$ ) than SVR patients. **Our results suggest** that immunomodulation fluctuates during antiviral treatment and that percentage CD81 expression levels on B cells and Tregs might be useful as an immunological prognostic factor for pegIFN- $\alpha$ 2a and ribavirin treatment response in chronic HCV infection.

**All-Cause, Liver-Related, and Non-Liver-Related Mortality Among HCV-Infected Individuals in the General US Population.** El-Kamary SS, Jhaveri R, Shardell MD. Clin Infect Dis. 2011 Jul;53(2):150-7. Epub 2011 Jun 10.

<http://www.ncbi.nlm.nih.gov/pubmed/21665867>

**BACKGROUND:** Liver-related mortality among those infected with hepatitis C virus (HCV) has been described, but little is known about non-liver-related mortality. Our objective was to determine HCV-associated all-cause, liver-, and non-liver-related mortality in the general US population. **METHODS:** A prospective cohort study of 9378 nationally representative adults aged 17-59 years was performed utilizing the Third National Health and Nutrition Examination Survey (NHANES III) Linked Mortality File that was made publicly available in 2010. HCV status was assessed from 1988 to 1994, with mortality follow-up of the same individuals through 2006. **RESULTS:** There were 614 deaths over a median follow-up of 14.8 years. After adjusting

for all covariate risk factors, HCV chronic infection had a 2.37 times higher all-cause mortality rate ratio [MRR] (95% CI: 1.28-4.38; P = .008), a 26.46 times higher liver-related MRR (95% CI: 8.00-87.48; P < .001), and 1.79 times higher non-liver-related MRR (95% CI: .77-4.19; P = .18), compared with being HCV-negative. This represents an estimated 2.46 million US adults aged 17-59 years with chronic HCV infection who had an estimated 31,163 deaths from all causes per year, of which 57.8% (95% CI: 21.9%-77.2%) were attributable to HCV. Among those, there was an estimated 9569 liver-related deaths per year, of which 96.2% (95% CI: 87.5-98.9%) were attributable to HCV. Non-liver-related deaths were not significantly associated with HCV status. **CONCLUSIONS:** Chronic HCV all-cause mortality is more than twice that of HCV-negative individuals. This suggests that those with chronic HCV infection are at a higher risk of death even after accounting for liver-related morbidity and should be closely monitored.

**Effect of combined siRNA of HCV E2 gene and HCV receptors against HCV.** Jahan S, Khaliq S, Samreen B, et al. *Virology*. 2011 Jun 10;8(1):295. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/21663667>

**BACKGROUND/AIM:** Hepatitis C virus (HCV) is a major threat as almost 3% of the world's population (350 million individual) and 10% of the Pakistani population is chronically infected with this virus. RNA interference (RNAi), a sequence-specific degradation process of RNA, has potential to be used as a powerful alternative molecular therapeutic approach in spite of the current therapy of interferon-alpha and ribavirin against HCV which has limited efficiency. HCV structural gene E2 is mainly involved in viral cell entry via attachment with the host cell surface receptors i.e., CD81 tetraspanin, low density lipoprotein receptor (LDLR), scavenger receptor class B type 1 (SR-B1), and Claudin1 (CLDN1). Considering the importance of HCV E2 gene and cellular receptors in virus infection and silencing effects of RNAi, the current study was designed to target the cellular and viral factors as new therapeutic options in limiting HCV infection. **RESULTS:** In this study the potential of siRNAs to inhibit HCV-3a replication in serum-infected Huh-7 cells was investigated by combined treatment of siRNAs against the HCV E2 gene and HCV cellular receptors (CD81 and LDLR), which resulted in a significant decrease in HCV viral copy number. **CONCLUSION:** From the current study it is concluded that the combined RNAi-mediated silencing of HCV E2 and HCV receptors is important for the development of effective siRNA-based therapeutic option against HCV-3a.

**Cyclosporine A-Based Immunosuppression Reduces Relapse Rate After Antiviral Therapy in Transplanted Patients With Hepatitis C Virus Infection: A Large Multicenter Cohort Study.** ReViS-TC Study Group. *Transplantation*. 2011 Jun 8. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/21659948>

**BACKGROUND:** The influence of immunosuppression on the response to antiviral treatment in recurrent hepatitis C is still under debate. The purpose of this study was to identify those factors that might predict sustained viral response and relapse. **METHODS:** The ReViS-TC, a multicenter cohort study conducted in 14 Spanish liver centers, included data from liver transplant recipients from January 2000 to December 2006 who had recurrent hepatitis C virus and who had undergone antiviral treatment with pegylated interferon plus ribavirin. Sustained virological response (SVR) and viral relapse were evaluated. A multivariate logistic regression model was used to investigate host, donor, and therapeutic factors associated with SVR and relapse. **RESULTS:** The analysis included 410 patients, 30% treated with cyclosporine A (CsA) and 70% with tacrolimus. SVR was achieved in 48% of patients with CsA and in 37% with

tacrolimus (P=0.037), with a relapse rate of 18% and 36%, respectively (P=0.006). In the multivariate model, the administration of CsA (odds ratio [OR] 0.37, P=0.021) in conjunction with a longer antiviral treatment duration (OR 0.86, P=0.024) correlated with lower relapse rate, whereas the older age of the donor (OR 1.03, P=0.006) and the presence of genotype 1 (OR 3.45, P=0.032) were associated with a higher probability of relapse. **CONCLUSIONS:** Our results suggest that the use of CsA-based immunosuppression regimens and longer treatment duration may protect patients against viral relapse after a positive response to pegylated interferon plus ribavirin therapy. These data need to be further confirmed in clinical trials.

**Randomised clinical trial: anti-viral activity of ANA773, an oral inducer of endogenous interferons acting via TLR7, in chronic HCV.** Bergmann JF, de Bruijne J, Hotho DM, et al. *Aliment Pharmacol Ther.* 2011 Jun 26. doi: 10.1111/j.1365-2036.2011.04745.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21707679>

**BACKGROUND:** The ANA773 is an oral prodrug of a small-molecule toll-like receptor (TLR)7 agonist. Preclinical and healthy volunteer clinical studies with ANA773 have demonstrated induction of endogenous interferon- $\alpha$  (IFN- $\alpha$ ) of multiple subtypes, which supports the potential utility in the treatment of chronic hepatitis C virus (HCV) infection. **Aim** To examine safety, tolerability, pharmacodynamics, pharmacokinetics and anti-viral activity of ANA773. **METHODS:** The ANA773 was investigated in a double-blind, placebo-controlled study in 34 patients chronically infected with HCV of any genotype. Patients were treatment-naïve or had relapsed following previous interferon-based treatment. This dose escalation study was composed of four dose groups (800, 1200, 1600 and 2000 mg). In each group, six to eight patients received ANA773 and two received placebo. Patients were dosed with ANA773 every-other-day for either 28 days (800, 1200 or 1600 mg) or 10 days (2000 mg). **RESULTS:** Mild to moderate adverse events were reported, with an increase in frequency and intensity with increasing dose. No serious AEs were reported and there were no early discontinuations. There were dose-related increases in various markers of IFN- $\alpha$  response. The mean maximum change in serum HCV RNA level from baseline was -0.34, -0.29, -0.40, -0.97 and -1.26 log(10) in the placebo, 800, 1200, 1600 and 2000 mg cohorts, respectively. At the 2000 mg dose, ANA773 significantly (P = 0.037) reduced serum HCV RNA levels (range: 0.14 to -3.10 log(10)). **CONCLUSION:** The ANA773 was generally well tolerated and resulted in a dose-related IFN-dependent response leading to a significant decrease in serum HCV RNA levels in the 2000 mg dose group.

**Genome-wide association study identified ITPA/DDRKG1 variants reflecting thrombocytopenia in pegylated interferon and ribavirin therapy for chronic hepatitis C.**

Tanaka Y, Kurosaki M, Nishida N, et al. *Hum Mol Genet.* 2011 Jun 23. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21659334>

Hematologic abnormalities during current therapy with pegylated interferon and ribavirin (PEG-IFN/RBV) for chronic hepatitis C (CHC) often necessitate dose reduction and premature withdrawal from therapy. **The aim of this study** was to identify host factors associated with IFN-induced thrombocytopenia by genome-wide association study (GWAS). In the GWAS stage using 900K single-nucleotide polymorphism (SNP) microarrays, 303 Japanese CHC patients treated with PEG-IFN/RBV therapy were genotyped. One SNP (rs11697186) located on DDRGK1 gene on chromosome 20 showed strong associations in the minor-allele-dominant

model with the decrease of platelet counts in response to PEG-IFN/RBV therapy [ $P = 8.17 \times 10(-9)$ ; odds ratio (OR) = 4.6]. These associations were replicated in another sample set ( $n = 391$ ) and the combined P-values reached  $5.29 \times 10(-17)$  (OR = 4.5). Fine mapping with 22 SNPs around DDRGK1 and ITPA genes showed that rs11697186 at the GWAS stage had a strong linkage disequilibrium with rs1127354, known as a functional variant in the ITPA gene. The ITPA-AA/CA genotype was independently associated with a higher degree of reduction in platelet counts at week 4 ( $P < 0.0001$ ), as well as protection against the reduction in hemoglobin, whereas the CC genotype had significantly less reduction in the mean platelet counts compared with the AA/CA genotype ( $P < 0.0001$  for weeks 2, 4, 8, 12), due to a reactive increase of the platelet count through weeks 1-4. **Our present results may provide** a valuable pharmacogenetic diagnostic tool for tailoring PEG-IFN/RBV dosing to minimize drug-induced adverse events.

**Prediction of Sustained Virological Response to Combination Therapy with Pegylated Interferon Alfa and Ribavirin in Patients with Genotype 3 Chronic Hepatitis C.** Tohra SK, Taneja S, Ghosh S, et al. Dig Dis Sci. 2011 Jun 25. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21706207>

**BACKGROUND:** Sustained virological response (SVR) rates in patients with hepatitis C are heterogeneous and are influenced by a wide range of host and viral factors. **AIM:** To evaluate the efficacy of combination therapy with pegylated interferon alfa (PEG-IFN- $\alpha$ ) and ribavirin (RBV), and document the SVR rates taking into consideration various predictive factors in patients with chronic hepatitis C (CHC) genotype 3. **METHODS:** Ninety-seven treatment-naive patients with CHC genotype 3 (mean age  $41.46 \pm 11.51$  years, M:F ratio 79:18), who received a combination of PEG-IFN ( $\alpha$ -2a or  $\alpha$ -2b) and RBV were retrospectively analyzed (2006-2008) for the early virological response (EVR) at 12 weeks, end of treatment response (ETR), and SVR at 6 months. **RESULTS:** Eighty-four (86.6%) patients achieved EVR and 81 (83.5%) achieved ETR, while SVR was achieved in 65 (67.0%) patients. Of the 84 patients who achieved EVR, 77 (91.7%) achieved ETR and 61 (72.6%) achieved SVR at 6 months. Age and body mass index (BMI) were found to be important predictors ( $*P < 0.05$ ) of SVR. CHC patients with a history of alcohol intake showed decreased SVR (52%) ( $*P = 0.035$ ) as compared to nonalcoholics (80%). Cirrhotic versus noncirrhotic patients showed no difference in SVR (54.5% vs. 70.7%) ( $P = 0.157$ ). Serum alanine aminotransferase (ALT) ( $P = 0.169$ ) and hepatitis C virus (HCV) RNA levels ( $P = 0.42$ ) also did not have an influence on the SVR. **CONCLUSION:** Combination therapy with PEG-IFN- $\alpha$  and RBV demonstrated good tolerability in CHC genotype 3 infection. Age, BMI, and alcohol consumption play an important role in determining treatment outcome.

**Retreatment of patients with chronic hepatitis C relapsers to a previous antiviral treatment.** Floreani A, Cazzagon N, Furlan P, et al. Eur J Gastroenterol Hepatol. 2011 Jun 4. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21654322>

**BACKGROUND:** The efficacy of retreatment with pegylated interferon (PEG-IFN) plus ribavirin for patients relapsing after a previous treatment remains to be fully elucidated, although extended treatment seems to be the best option in such cases. **AIM:** To evaluate the efficacy of two extended protocols in patients with genotypes 1 or 4, or those with genotypes 2 or 3. **METHODS:** A total of 181 patients who had relapsed after a previous antiviral treatment with PEG-IFN $\alpha$ 2a plus weight-based ribavirin were offered retreatment with the same dose of both PEG-IFN plus ribavirin, to be continued for 48 weeks in those with genotypes 2 or 3 (group 1),

and for 72 weeks in those with genotypes 1 or 4 (group 2). **RESULTS:** A total of 59 patients (32.5%) refused the retreatment, while 122 (78 men, 44 women) patients were enrolled in the study: 41 were allocated in group 1 and 81 in group 2. Cirrhosis at baseline (staging 5/6 according to Ishak's score was recorded in 11 patients, six in group 1 and five in group 2). Nine patients (7.3%) in group 2 discontinued the treatment (due to lack of response). The remaining patients completed the treatment and were followed-up for at least 12 months after the treatment. Sustained virological response (SVR) rate was 82.9% in group 1 and 50.6% in group 2. **CONCLUSION:** Patients with chronic hepatitis C with 'easy genotypes' relapsers to a previous antiviral treatment have more than 80% probability of achieving a SVR with a 48-week retreatment. Patients with 'difficult genotypes' have more than 50% chance of a SVR after a 72-week extended treatment.

**Peginterferon Alfa-2a Is Superior to Peginterferon Alfa-2b in the Treatment of Naïve Patients with Hepatitis C Virus Infection: Meta-Analysis of Randomized Controlled Trials.** Singal AK, Jampana SC, Anand BS. Dig Dis Sci. 2011 Jun 4. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21643737>

**BACKGROUND:** Pegylated interferon (PEGIFN) and ribavirin combination is the standard of care for the treatment of chronic hepatitis C virus (HCV) infection. Studies comparing the efficacy and safety of PEGIFN alfa-2a and PEGIFN alfa-2b in treatment-naïve HCV-infected patients have shown conflicting results. **AIM:** We performed a systematic review and meta-analysis of studies comparing the efficacy and safety of PEGIFN alfa-2a and PEGIFN alfa-2b in HCV-infected patients naïve to treatment. **METHODS:** Nine studies (five abstracts) with 3,546 patients (1,771 treated with PEGIFN alfa-2a) comparing PEGIFN alfa-2a and PEGIFN alfa-2b in treatment-naïve HCV patients were analyzed. Efficacy outcomes were sustained virologic response (SVR) and treatment discontinuation rates due to serious adverse effects (SAE).

**RESULTS:** Pooled data on outcomes (reported as odds ratios [ORs] with 95% confidence intervals [CIs]: [OR (95% CI)]) showed higher SVR in patients treated with PEGIFN alfa-2a as compared to treatment with PEGIFN alfa-2b [1.36 (1.07-1.73); P = 0.01]. Subgroup analysis of good quality studies on SVR in genotypes 2 and 3 also favored PEGIFN alfa-2a over PEGIFN alfa-2b (1.91 [1.09-3.37]; P = 0.02). SVR results obtained with the two types of IFN showed no impact of viral load and the presence or absence of cirrhosis. Treatment discontinuation rates due to SAE, reported in six studies (two abstracts) on 3,211 patients (1,604 treated with PEGIFN alfa-2a), were similar in the two types of PEGIFN [0.66 (0.37-1.16); P = 0.15].

**CONCLUSIONS:** PEGIFN alfa-2a has superior efficacy with higher SVR as compared to PEGIFN alfa-2b in treatment-naïve HCV-infected patients. The safety profile of the two types of PEGIFN was similar.

**Retreatment of Hepatitis C with Consensus Interferon and Ribavirin After Nonresponse or Relapse to Pegylated Interferon and Ribavirin: A National VA Clinical Practice Study.**

Yee HS, Currie SL, Tortorice K, et al. Dig Dis Sci. 2011 Jun 2. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21633833>

**BACKGROUND:** Studies of the retreatment with consensus interferon (CIFN) and ribavirin (RBV) of hepatitis C virus (HCV)-infected patients who failed prior pegylated interferon alfa/ribavirin (PEG-IFN/RBV) have found quite variable efficacy and tolerability of this therapy. As such, CIFN/RBV use and efficacy in clinical practice were evaluated within the Department of Veterans Affairs (VA), the largest national, integrated system for HCV care.

**AIMS:** The purpose of this study was to determine rates of sustained virologic response (SVR) and patterns of CIFN/RBV use in the VA. Methods included retrospective review of national VA data in HCV-infected patients who had previously failed  $\geq 12$  weeks of PEG-IFN/RBV and were prescribed CIFN/RBV between October 1, 2003 and September 30, 2006. **RESULTS:** A total of 597 patients met the study criteria. CIFN was primarily dosed as 15 mcg subcutaneously daily combined with standard doses of RBV. Mean treatment duration was 21 weeks; CIFN was discontinued within 4 weeks in 24%. Hematological growth factors were used in 49%. Post-treatment viral loads were available in 385 patients. SVR to CIFN/RBV was achieved in 11%, and was significantly higher in prior PEG-IFN/RBV relapsers compared with nonresponders (31% vs. 6%, respectively;  $P < 0.0001$ ). A 2-log(10) or greater drop in HCV RNA after 24 weeks of PEG-IFN/RBV was a predictor of subsequent SVR to CIFN/RBV.

**CONCLUSIONS:** CIFN/RBV was used frequently in clinical practice for retreatment of PEG-IFN/RBV. In this setting, early treatment discontinuation was common. Overall SVR was low, although response was significantly better in prior PEG-IFN/RBV relapsers and those who had a 2-log(10) or greater decline than in nonresponders.

**Role of Interleukin 28B rs12979860 C/T Polymorphism on the Histological Outcome of Chronic Hepatitis C: Relationship with Gender and Viral Genotype.** Falletti E, Bitetto D, Fabris C, et al. J Clin Immunol. 2011 Jun 7. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21647799>

**BACKGROUND:** This study aimed to determine whether the single-nucleotide polymorphism (rs12979860 C/T) of the interleukin 28B (IL-28B) gene, which is associated with hepatitis C virus (HCV) clearance, is also associated with fibrosis in chronic HCV infection. **METHODS:** An RFLP-PCR technique was used to genotype 629 HCV-positive patients (200 with cirrhosis) and 428 healthy control subjects. **RESULTS:** The genotype frequencies in the controls and chronic hepatitis C patients were as follows: C/C 47.0% vs. 32.6%, C/T 41.8% vs. 52.8% and T/T 11.2% vs. 14.6% ( $p < 0.0001$ ). The C allele frequency was higher in HCV-2- (0.635) and 3- (0.692) infected patients in comparison to those infected with HCV-1 (0.550) or 4-5 (0.600) ( $p < 0.001$ ). Infected T/T homozygotes had a mean staging score higher than other patients (3.50 vs. 3.04,  $p < 0.05$ ). **CONCLUSIONS:** IL-28B rs12979860 C/T polymorphism is associated with a greater likelihood of HCV persistence, particularly in HCV genotypes 1 and 4. The T allele affects the severity of liver fibrosis.

**Serodiagnosis of Helicobacter hepaticus infection in patients with liver and gastrointestinal diseases: western blot analysis and ELISA using a highly specific monoclonal antibody for H. hepaticus antigen.** Murakami K, Takahashi R, Ono M, et al. J Gastroenterol. 2011 Jun 8. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21656014>

**BACKGROUND:** Helicobacter hepaticus infection might be associated with liver and biliary tract diseases. To investigate its pathogenic role, the properties of anti-H. hepaticus serum antibody in patients with liver and diseases were elucidated. **METHODS:** Serum samples were collected from 166 patients-69 with liver diseases, 38 with upper gastrointestinal diseases, 17 with lower gastrointestinal diseases, 26 with biliary tract diseases, and 16 with pancreas diseases; 30 control sera were obtained from 30 healthy blood donors. Serum samples were analyzed by enzyme-linked immunosorbent assay (ELISA) and western blot using the new monoclonal antibody HR II-51. **RESULTS:** Anti-H. hepaticus serum antibody concentrations in patients

with liver disease (n = 69) were significantly increased compared with those in other disease groups (p = 0.014 to <0.001). Particularly, liver cirrhosis (n = 19) showed a significantly higher antibody level compared with other liver diseases (n = 50, p = 0.005) and healthy donors (n = 30, p = 0.0005), as well as a higher seroprevalence (68.4%) compared with other liver diseases (p = 0.05) and healthy donors (p = 0.004). Furthermore, the ELISA value in liver cirrhosis (n = 19) was significantly higher than that in patients with hepatitis B virus (HBV)-and/or hepatitis C virus (HCV)-infected chronic hepatitis (n = 15) ( $0.389 \pm 0.084$  vs.  $0.350 \pm 0.084$ , p = 0.029). However, there was no relationship between the total immunoglobulin concentration and the anti-H. hepaticus antibody level in each liver disease (Spearman's rank correlation coefficient [rs] < 0.225). **CONCLUSIONS:** H. hepaticus infection might play a role in the development of liver diseases; in particular, it might increase the risk of the development of HBV- and/or HCV-infected liver diseases.

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## BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

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**Common genetic polymorphism of ITPA gene affects ribavirin-induced anemia and effect of peg-interferon plus ribavirin therapy.** Azakami T, Hayes CN, Sezaki H, et al. J Med Virol. 2011 Jun;83(6):1048-57. doi: 10.1002/jmv.22069.

<http://www.ncbi.nlm.nih.gov/pubmed/21503919>

An association between a single nucleotide polymorphism (SNP) in the inosine triphosphate pyrophosphatase (ITPA) gene and reduction of hemoglobin during peg-interferon plus ribavirin combination therapy for patients with chronic hepatitis C virus (HCV) infection has been reported. However, the effect of the SNP on outcome of therapy has not been fully elucidated. Factors associated with anemia during combination therapy, including rs1127354 genotype, were analyzed in 1,002 treated patients. The effect of the SNP on outcome of therapy was analyzed in a subset of 830 patients with genotype 1. A rapid initial decrease in hemoglobin levels was observed in patients with rs1127354 genotype CC compared with a slow decrease in non-CC patients. Cumulative reduction of ribavirin was significantly more frequent in genotype CC patients than non-CC patients (odds ratio 1.928, P =  $8.6 \times 10^{-8}$ ). The frequency of patients who received at least the recommended 80% of scheduled ribavirin was significantly lower among genotype CC patients, especially among those who had pretreatment hemoglobin levels between 13.5 and 15 g/dl (P < 0.03), and the sustained viral response rate was significantly lower in this group of patients. Independent predictive factors for sustained virological response included a SNP in the IL28B locus (rs809991), age, fibrosis, ITPA SNP rs1127354 as well as pretreatment hemoglobin levels. Our data suggests that measures to prevent anemia should be considered for patients who have pretreatment hemoglobin levels less than 13.5 g/dl or who have rs1127354 genotype CC and pretreatment hemoglobin levels between 13.5 and 15 g/dl.

**Low doses of the novel caspase-inhibitor GS-9450 leads to lower caspase-3 and -8 expression on peripheral CD4+ and CD8+ T-cells.** Arends JE, Hoepelman AI, Nanlohy NM, et al. Apoptosis. 2011 Jun 11. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21667042>

Chronic hepatitis C virus (HCV) infection is characterized by increased rates of apoptotic hepatocytes and activated caspases have been shown in HCV-infected patients. GS-9450, a novel caspase-inhibitor has demonstrated hepatoprotective activity in fibrosis/apoptosis animal models. This study evaluated the effects of GS-9450 on peripheral T-cell apoptosis in chronic HCV-

infected patients. As sub study of the GS-US-227-0102, a double-blind, placebo-controlled phase 2a trial evaluating the safety and tolerability of GS-9450, apoptosis of peripheral CD4+ and CD8+ T-cells was measured using activated caspase-3, activated caspase-8 and CD95 (Fas). Blood samples were drawn at baseline, day 14 after therapy and at 5 weeks off-treatment follow-up in the first cohort of 10 mg. In contrast to the placebo-treated patients, GS-9450 caused a median of 46% decrease in ALT-values from baseline to day 14 in all treated patients (median of 118-64 U/l) rising again to a median of 140 U/l (19%) at 5 weeks off-treatment follow-up. In GS9450-treated patients, during treatment and follow-up, percentages of activated caspase-3+ and caspase-8 expression tended to decrease, in contrast to placebo-treated patients. Interestingly, compared to healthy controls, higher percentages of caspase-3 and caspase-8 positive CD4+ and CD8+ T-cells were demonstrated in HCV-infected patients at baseline. Decreased ALT-values were observed in all HCV-infected patients during treatment with low dose of the caspase-inhibitor GS-9450 accompanied by a lower expression of caspase-3 and -8 on peripheral T-cells. Furthermore, at baseline percentages of activated caspase-3, activated caspase-8 and CD95+ T-cells were higher in chronic HCV-infected patients compared to healthy controls.

**Preexisting drug-resistance mutations reveal unique barriers to resistance for distinct antivirals.** Robinson M, Tian Y, Delaney WE 4th, Greenstein AE. Proc Natl Acad Sci U S A. 2011 Jun 21;108(25):10290-5. Epub 2011 Jun 6.

<http://www.ncbi.nlm.nih.gov/pubmed/21646519>

Clinical trials of direct-acting antiviral agents in patients chronically infected with hepatitis C virus (HCV) have demonstrated that viral resistance is detected rapidly during monotherapy. In patients, HCV does not exist as a single, genetically homogenous virus but rather as a population of variants termed "quasispecies." Preexisting variants resistant to specific antiviral drugs, overlooked in traditional hit-to-lead discovery efforts, may be responsible for these poor clinical outcomes. To enable real-time studies of resistance emergence in live cells, we established fluorescent protein-labeled HCV replicon cell lines. We validated these cell lines by demonstrating that antiviral susceptibility and the selection of signature resistance mutations for various drug classes are similar to traditional replicon cell lines. By quantifying the kinetics and uniformity of replication within colonies of drug-resistant fluorescent replicon cells, we showed that resistance emerged from a single cell and preexisted in a treatment-naive replicon population. Within this population, we determined the relative frequency of preexisting replicons capable of establishing foci during treatment with distinct antivirals. By measuring relative frequency as a function of dose, we quantitatively ranked distinct antiviral molecules on the basis of their distinct barriers to resistance. These insights into RNA virus quasispecies structure provide guidance for selecting clinical drug concentrations and selecting antiviral drug combinations most likely to suppress resistance.

**Effects of hepatitis C virus on suppressor of cytokine signaling mRNA levels: comparison between different genotypes and core protein sequence analysis.** Pascarella S, Clément S, Guilloux K, Conzelmann S, Penin F, Negro F. J Med Virol. 2011 Jun;83(6):1005-15. doi: 10.1002/jmv.22072.

<http://www.ncbi.nlm.nih.gov/pubmed/21503913>

Glucose metabolism disturbances, including insulin resistance and type 2 diabetes, are frequent and important cofactors of hepatitis C. Increasing epidemiological and experimental data suggest

that all major genotypes of hepatitis C virus (HCV), albeit to a different extent, cause insulin resistance. The HCV core protein has been shown to be sufficient to impair insulin signaling in vitro through several post-receptorial mechanisms, mostly via the activation of suppressor of cytokine signaling (SOCS) family members and the consequent decrease of insulin receptor substrate-1 (IRS-1). The levels of IRS-1 and SOCS were investigated upon expression of the core protein of HCV genotypes 1-4. Furthermore, the core protein sequences were analyzed to identify the amino acid residues responsible for IRS-1 decrease, with particular regard to SOCS mRNA deregulation. The results suggest that the activation of SOCS family members is a general mechanism associated with the common HCV genotypes. A rare genotype 1b variant, however, failed to activate any of the SOCS tested: this allowed to analyze in detail the distinct amino acid sequences responsible for SOCS deregulation. By combining approaches using intergenotypic chimeras and site-directed mutagenesis, genetic evidence was provided in favor of a role of amino acids 49 and 131 of the HCV core-encoding sequence in mediating SOCS transactivation.

**A genetically humanized mouse model for hepatitis C virus infection.** Dorner M, Horwitz JA, Robbins JB, et al. *Nature*. 2011 Jun 8;474(7350):208-11. doi: 10.1038/nature10168.  
<http://www.ncbi.nlm.nih.gov/pubmed/21654804>

Hepatitis C virus (HCV) remains a major medical problem. Antiviral treatment is only partially effective and a vaccine does not exist. Development of more effective therapies has been hampered by the lack of a suitable small animal model. Although xenotransplantation of immunodeficient mice with human hepatocytes has shown promise, these models are subject to important challenges. Building on the previous observation that CD81 and occludin comprise the minimal human factors required to render mouse cells permissive to HCV entry in vitro, we attempted murine humanization via a genetic approach. Here we show that expression of two human genes is sufficient to allow HCV infection of fully immunocompetent inbred mice. We establish a precedent for applying mouse genetics to dissect viral entry and validate the role of scavenger receptor type B class I for HCV uptake. We demonstrate that HCV can be blocked by passive immunization, as well as showing that a recombinant vaccinia virus vector induces humoral immunity and confers partial protection against heterologous challenge. This system recapitulates a portion of the HCV life cycle in an immunocompetent rodent for the first time, opening opportunities for studying viral pathogenesis and immunity and comprising an effective platform for testing HCV entry inhibitors in vivo.

**Sequence heterogeneity of NS5A and core proteins of hepatitis C virus and virological responses to pegylated-interferon/ribavirin combination therapy.** El-Shamy A, Shoji I, Saito T, et al. *Microbiol Immunol*. 2011 Jun;55(6):418-26. doi: 10.1111/j.1348-0421.2011.00331.x.  
<http://www.ncbi.nlm.nih.gov/pubmed/21371092>

Both host and viral factors have been implicated in influencing the response to pegylated-interferon/ribavirin (PEG-IFN/RBV) therapy for hepatitis C virus (HCV) infection. Among the viral factors, sequence heterogeneity within NS5A and core regions has been proposed. This study aimed to clarify the relationship between virological responses to PEG-IFN/RBV therapy and sequence heterogeneity within NS5A, including the IFN/RBV resistance-determining region (IRRDR), the interferon sensitivity-determining region (ISDR) and the core region. Pretreatment sequences of NS5A and the core regions were analyzed in 57 HCV-1b-infected patients who were to be treated with PEG-IFN/RBV. Of 40 patients infected with HCV having an IRRDR

with four or more mutations ( $IRRDR \geq 4$ ), 28 (70%) patients achieved a sustained virological response (SVR). On the other hand, only 4 (24%) of 17 patients infected with HCV having an  $IRRDR$  with three or fewer mutations ( $IRRDR \leq 3$ ) achieved a SVR ( $P= 0.001$ ). Similarly, 22 (71%) of 31 patients infected with HCV and having an  $ISDR$  with one or more mutations ( $ISDR \geq 1$ ) achieved a SVR while 10 (38%) of 26 patients infected with HCV and having an  $ISDR$  without any mutations ( $ISDR = 0$ ) achieved a SVR ( $P= 0.014$ ). As for the core region, there was significant correlation between a single mutation at position 70 (Gln(70) ) and non-SVR ( $P= 0.02$ ). Notably, Gln(70) was more prominently associated with the null response ( $P= 0.0007$ ). **In conclusion**, sequence heterogeneity within the  $IRRDR$  and  $ISDR$ , and a single point mutation at position 70 of the core region of HCV-1b are likely to be correlated with virological responses to PEG-IFN/RBV therapy.

**Neurotoxic effects of the HCV core protein are mediated by sustained activation of ERK via TLR2 signaling.** Paulino AD, Ubhi K, Rockenstein E, et al. J Neurovirol. 2011 Jun 10. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21660601>

Hepatitis C virus (HCV) infection is a serious problem among those co-infected with human immunodeficiency virus; however, its impact in the central nervous system (CNS) remains unclear. This study aimed to investigate the mechanisms underlying HCV core protein-mediated neurodegeneration. Analysis of human HCV seropositive cases demonstrated widespread damage to neuronal dendritic processes and sustained activation of extracellular signal-related kinase (ERK); analogous pathologies were observed in wild type injected with HCV core protein into the hippocampus. In vitro analysis in neuronal cells exposed to HCV core demonstrated retraction of the neuronal processes in an ERK/Signal Transducer and Activator of Transcription 3 (STAT3)-dependent manner dependent on toll-like receptor 2 (TLR2) signaling activation. These results indicate that HCV core protein neurotoxicity may be mediated by the sustained activation of ERK/STAT3 via TLR2-IRAK1 signaling pathway. These pathways provide novel targets for development of neuroprotective treatments for HCV involvement of the CNS.

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## HIV/HCV/HBV COINFECTION

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**Molecular characterization of hepatitis C virus genotype 4 sequences in HIV-coinfected patients from Argentina.** Bolcic F, Jones LR, Laufer N, Quarleri J. J Med Virol. 2011 Jun;83(6):935-40. doi: 10.1002/jmv.22068.

<http://www.ncbi.nlm.nih.gov/pubmed/21503903>

The prevalence of hepatitis C virus genotype 4 (HCV-4) is increasing in different parts of the World but in Latin America the data are still scarce. We aimed to characterize HCV-4 isolates from 383 HIV-coinfected patients in Argentina. Sequence analyses were based on the non-structural 5B region of HCV. Results from 18 patients indicated a genetic heterogeneity that involved three genotype 4 subtypes. Sequences were ascribed to subtype 4d (67%), 4a (22%), and 4m (11%). In spite of different sources of transmission were defined among patients, no statistical association was found with the genotype 4 subtype. The scenario is also compatible with multiple importation of the epidemic and there is no evidence for transmission-specific clusters or network-like transmission of HCV-4. This HCV-4 does not represent a recent introduction in Argentina, it circulates in all transmission groups and its presence is increasing among HIV-infected patients.

**Liver Toxicity of Antiretroviral Combinations Including Fosamprenavir Plus Ritonavir 1400/100 mg Once Daily in HIV/Hepatitis C Virus-Coinfected Patients.** Merchante N, López-Cortés LF, Delgado-Fernández M, et al. AIDS Patient Care STDS. 2011 Jun 20. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21688986>

Our objective was to evaluate the liver toxicity of antiretroviral regimens including fosamprenavir plus ritonavir (FPV/r) 1400/100 mg once daily (QD) in HIV/hepatitis C virus (HCV)-coinfected patients. This was a prospective cohort study that included 117 HIV/HCV-coinfected patients who started FPV/r 1400/100 mg QD-based antiretroviral therapy (ART) and who neither had received a previous antiretroviral regimen containing FPV nor had a past history of virologic failure while receiving protease inhibitors (PI). The primary end point of the study was the occurrence of grade 3-4 liver enzymes elevations (LEE) within 1 year after starting FPV/r QD. Factors potentially associated with grade 3-4 LEE, including baseline liver fibrosis, were analyzed. Eleven (9%) patients had a grade 3-4 LEE during the follow-up, resulting in an incidence of severe liver toxicity of 9% (95% confidence interval 4.1-14.6%). None of these cases led to FPV/r discontinuation. Baseline liver fibrosis could be assessed in 97 (83%) patients. Six of 71 patients (8%) with significant fibrosis had a grade 3-4 LEE versus 2 of 26 (8%) without significant fibrosis ( $p=1.0$ ). Twenty (21%) patients had cirrhosis at baseline. There were no cases of LEE among cirrhotics. In conclusion, the incidence of severe liver toxicity after 1 year of therapy with FPV/r QD-based ART in HIV/HCV-coinfected patients is similar to what has been reported with other boosted PIs. In addition, the presence of significant fibrosis or cirrhosis was not associated with the emergence of liver toxicity. Thus, ART regimens containing FPV/r QD may be considered safe in HIV/HCV-coinfected patients, including those with cirrhosis.

**Do rates of unprotected anal intercourse among HIV-positive MSM present a risk for hepatitis C transmission?** Stall R, Wei C, Raymond HF, McFarland W. Sex Transm Infect. 2011 Jun 8. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21653934>

**OBJECTIVES:** To compare the rates of unprotected anal intercourse (UAI) among men who have sex with men (MSM) in HIV-seropositive sexual relationships with that among men in HIV-seronegative and serodiscordant relationships in the context of an emerging hepatitis C virus (HCV) epidemic among HIV-positive MSM. **METHODS:** Time-location sampling was used to obtain a cross-sectional sample of MSM who attended public venues in San Francisco between November 2007 and October 2008 (N=1199). Behavioural measures of sexual risk-taking at the level of the sexual dyad were administered to the sample. **RESULTS:** Men in HIV-positive/positive sexual relationships are significantly more likely to have UAI and combine sex and drugs than men in negative/negative sexual relationships. **CONCLUSIONS:** If it is possible to spread HCV infection between HIV-positive men via UAI, very high levels of behavioural risk among positive MSM should exist to facilitate HCV transmission. Identifying the precise behavioural risk factors for HCV among HIV-positive MSM has become an important public health priority.

**Presence of occult HBV, but near absence of active HBV and HCV infections in people infected with HIV in rural South Africa.** Barth RE, Huijgen Q, Tempelman HA, et al. *J Med Virol.* 2011 Jun;83(6):929-34. doi: 10.1002/jmv.22026.

<http://www.ncbi.nlm.nih.gov/pubmed/21503902>

Human immunodeficiency (HIV), hepatitis B (HBV), and hepatitis C (HCV) viruses are endemic in Sub-Saharan Africa, but data regarding the prevalence of hepatitis co-infections in HIV-positive individuals residing there are limited. The aim of the study was to determine the prevalence of HBV, HCV, and occult HBV (presence of HBV-DNA in the absence of HBsAg) in a rural, South African cohort. The results were compared to various ethnic groups in a Dutch cohort of people infected with HIV. Antiretroviral-naïve individuals with HIV from both a rural South African clinic (n = 258), and a Dutch University hospital (n = 782), were included. Both serological (HBV and HCV) and molecular (occult HBV) assays were performed. Logistic regression analysis was used to define independent predictors of a hepatitis co-infection. HBV and HCV prevalence rates in the South African cohort were exceptionally low (0.4%, 1/242 and 0.8%, 2/242, respectively), compared to those observed in Caucasians (HBV 4.4% and HCV 10.9%) and African immigrants (HBV 8.9% and HCV 4.8%). Conversely, occult HBV was observed in a considerable proportion (10%, 6/60) of South African patients who were anti-HBc-positive but HBsAg-negative. Occult infections were less frequent in Caucasians and Africans in the Dutch cohort (3.2% and 1.4%, respectively). Independent predictors for occult HBV were not identified, but a trend towards more occult HBV at lower CD4 counts was observed. Local HBV/HCV prevalence data are needed to optimize vaccination and antiretroviral treatment strategies. Occult HBV in patients with HIV may be missed regularly when molecular analyses are not available.

**Ethnic differences in viral dominance patterns in patients with hepatitis B virus and hepatitis C virus dual infection.** Nguyen LH, Ko S, Wong SS, et al. *Hepatology.* 2011 Jun;53(6):1839-45. doi: 10.1002/hep.24308.

<http://www.ncbi.nlm.nih.gov/pubmed/21425314>

Studies of hepatitis B virus (HBV)/hepatitis C virus (HCV) dual infection are limited. Most are small, conducted outside the United States, and compare dual infection with HCV mono-infection. **The goal of this study** was to characterize HBV/HCV dual infection in a large multiethnic, matched, case-control study of dual-infected and HBV-mono-infected patients at two United States centers. Using an International Classification of Disease Version 9 electronic query and chart review, we identified 115 HBV/HCV dual-infected patients with serial HBV DNA, HCV RNA, and alanine aminotransferase (ALT) levels. As a control, 115 HBV-mono-infected patients were chosen randomly and matched with cases by age  $\pm 10$  years, sex, Asian versus non-Asian ethnicity, and study site. Both groups had similar sex, ethnic, and age distributions (68% male, 83% Asian, age  $52 \pm 14$  years). The median follow-up times were 33 and 38 months for the dual-infected and mono-infected groups, respectively. More mono-infected patients received HBV antiviral therapy than dual-infected patients (43% versus 24%;  $P = 0.002$ ). No significant difference was detected between the proportion of mono-infected versus dual-infected patients with ALT above 40 U/L at presentation or during follow-up. Dual infection patients exhibited very little HBV/HCV codominance at baseline and throughout follow-up: patients had either HBV viremia with low or absent HCV RNA or detectable HCV RNA with low or absent HBV DNA. Asian ethnicity was predictive of HBV dominance after adjusting for sex, age, and baseline ALT elevation (odds ratio 7.35;  $P = 0.01$ ). **CONCLUSION:** HBV/HCV dual-infected

and HBV-monoinfected patients had similar clinical characteristics. Asian ethnicity is a major independent predictor of HBV-dominant disease, and HCV dominance with undetectable HBV DNA is more common in non-Asian individuals. Larger studies are needed to further characterize the natural history of HBV/HCV dual infection in Asian and non-Asian individuals.

**The Relation of HLA Genotype to Hepatitis C Viral Load and Markers of Liver Fibrosis in HIV-Infected and HIV-Uninfected Women.** Kuniholm MH, Gao X, Xue X, et al. J Infect Dis. 2011 Jun;203(12):1807-14.

<http://www.ncbi.nlm.nih.gov/pubmed/21606539>

**BACKGROUND:** Human leukocyte antigen (HLA) class I and II genotype is associated with clearance of hepatitis C virus (HCV) infection, but little is known regarding its relation with HCV viral load or risk of liver disease in patients with persistent HCV infection. **METHODS:** High-resolution HLA class I and II genotyping was conducted in a prospective cohort of 519 human immunodeficiency virus (HIV)-seropositive and 100 HIV-seronegative women with persistent HCV infection. The end points were baseline HCV viral load and 2 noninvasive indexes of liver disease, fibrosis-4 (FIB-4), and the aspartate aminotransferase to platelet ratio index (APRI), measured at baseline and prospectively. **RESULTS:** DQB1\*0301 was associated with low baseline HCV load ( $\beta = -.4$ ; 95% confidence interval [CI],  $-.6$  to  $-.3$ ;  $P < .00001$ ), as well as with low odds of FIB-4-defined (odds ratio [OR],  $.5$ ; 95% CI,  $.2$ - $.9$ ;  $P = .02$ ) and APRI-defined liver fibrosis (OR,  $.5$ ; 95% CI,  $.3$ - $1.0$ ;  $P = .06$ ) at baseline and/or during follow-up. Most additional associations with HCV viral load also involved HLA class II alleles. Additional associations with FIB-4 and APRI primarily involved class I alleles, for example, the relation of B\*1503 with APRI-defined fibrosis had an OR of 2.0 (95% CI,  $1.0$ - $3.7$ ;  $P = .04$ ). **CONCLUSIONS:** HLA genotype may influence HCV viral load and risk of liver disease, including DQB1\*0301, which was associated with HCV clearance in prior studies.

**Concomitant Highly Active Antiretroviral Therapy Leads to Smaller Decline and Faster Recovery of CD4+ Cell Counts During and After Pegylated Interferon Plus Ribavirin Therapy in HIV-Hepatitis C Virus Coinfected Patients.** Reiberger T, Payer BA, Kosi L, et al. J Infect Dis. 2011 Jun;203(12):1802-1806.

<http://www.ncbi.nlm.nih.gov/pubmed/21606538>

**INTRODUCTION:** The impact of highly active antiretroviral therapy (HAART) on CD4+ cell course during treatment with pegylated interferon plus ribavirin (PegIFN-RBV) in patients coinfecting with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) is unknown. **METHODS:** We determined CD4(+) cell count in 94 HIV-HCV coinfecting patients undergoing treatment with pegylated interferon plus RBV at baseline, treatment weeks 4-48 (W4-W48), and months 1, 3, and 6 of follow-up. Of the 94 patients, 70 underwent concomitant HAART (group A) and 24 did not (group B). **RESULTS:** Group A showed smaller CD4(+) cell decreases from W24-W48 ( $P = .027$ ) and greater CD4(+) cell increases after cessation of pegylated interferon plus ribavirin therapy ( $P = .002$ ) than group B showed. **CONCLUSIONS:** Concomitant HAART leads to smaller decreases and faster recovery of CD4(+) cells during and after pegylated interferon plus RBV therapy.

**Twice-weekly pegylated interferon- $\alpha$ -2a and ribavirin results in superior viral kinetics in HIV/hepatitis C virus co-infected patients compared to standard therapy.** Murphy AA, Herrmann E, Osinusi AO, et al. AIDS. 2011 Jun 1;25(9):1179-1187.

<http://www.ncbi.nlm.nih.gov/pubmed/21593619>

**BACKGROUND:** Hepatitis C virus (HCV)/HIV co-infected patients have more rapid progression of liver fibrosis and only modest cure rates (sustained virologic responses, SVRs) when compared to HCV monoinfected patients. **METHOD:** We compared the virologic responses of either twice-weekly peginterferon- $\alpha$ -2a 180  $\mu$ g/week (for 4 weeks, followed by weekly dosing) or weekly peginterferon- $\alpha$ -2a 180  $\mu$ g/week, and weight-based ribavirin (1-1.2 g/day), among HIV/HCV co-infected genotype-1 individuals. **RESULTS:** Patients receiving the investigational dosing had lower levels of HCV RNA at all time points after initiation of therapy. More patients on this arm achieved clinically relevant early virological responses at weeks 1, 2, 4, 12, and 24. The enhanced early virologic response observed with the investigational arm was associated with a higher induction of interferon-stimulated genes. This early double dose regimen also resulted in a rapid normalization of liver enzymes. Twice-weekly peginterferon- $\alpha$ -2a was associated with more frequent early virological responses with similar safety profiles when compared with standard therapy. **CONCLUSION:** Our results, when confirmed in larger randomized clinical trials, may provide a novel therapeutic approach to improve SVR among HIV/HCV co-infected patients, especially African-American patients.

**Influence of Interleukin-28B Single-Nucleotide Polymorphisms on Progression to Liver Cirrhosis in Human Immunodeficiency Virus-Hepatitis C Virus-Coinfected Patients Receiving Antiretroviral Therapy.** Barreiro P, Pineda JA, Rallón N, et al. J Infect Dis. 2011 Jun;203(11):1629-36.

<http://www.ncbi.nlm.nih.gov/pubmed/21592993>

**BACKGROUND:** Single-nucleotide polymorphisms (SNPs) near the IL28B gene have recently been associated with spontaneous hepatitis C virus (HCV) clearance and response to interferon-based therapies in patients with chronic hepatitis C. Because human immunodeficiency virus (HIV) coinfection appears to accelerate HCV-related liver fibrosis progression, any influence of IL28B SNP on the risk of developing cirrhosis might be more easily recognized in the coinfecting population. **METHODS:** All HIV-HCV-coinfecting patients who underwent hepatic elastography before initiating a course of pegylated interferon plus ribavirin therapy at 2 Spanish clinics were retrospectively identified. Liver cirrhosis was defined as  $>14.5$  kPa by transient elastography. The IL28B rs12979860 SNP was examined in a blinded fashion. **RESULTS:** A total of 304 HIV-HCV-coinfecting individuals were analyzed (mean age, 43 years; 80% were male; and 85% were receiving antiretroviral therapy), of whom 18% had cirrhosis. IL28B genotype distribution was as follows: CC, 46%; CT, 43%; and TT, 11%. Cirrhosis was more frequent in CC than CT/TT carriers (24% vs 13%;  $P = .01$ ). Logistic regression analysis revealed that older age (odds ratio [OR], 1.05; 95% confidence interval [CI], 0.99-1.12);  $P = .08$ ), past alcohol abuse (OR, 1.97; 95% CI, 0.95-4.06;  $P = .07$ ), and CC IL28B genotype (OR, 2.32; 95% CI, 1.22-4.41;  $P = .01$ ) were predictors of cirrhosis. Interestingly, mean (SD) alanine aminotransferase (ALT) levels were greater ( $90 \pm 53$  vs  $71 \pm 33$  IU/L;  $P = .01$ ) in IL28B CC than CT/TT carriers during the prior  $4.8 \pm 3.8$  years. **CONCLUSIONS:** The IL28B rs12979860 CC genotype is associated with a higher prevalence of cirrhosis in HIV-HCV-coinfecting patients than CT/TT genotypes, suggesting that IL28B CC carriers may experience a more rapid progression of HCV-related liver fibrosis, perhaps as result of increased liver inflammation. Thus, access to HCV treatment is of utmost importance in IL28B CC carriers, in whom treatment response is better and in whom progression to cirrhosis might occur more rapidly.

**Estimated Risk of Human Immunodeficiency Virus and Hepatitis C Virus Infection among Potential Organ Donors from 17 Organ Procurement Organizations in the United States.**

Ellingson K, Seem D, Nowicki M, et al. Am J Transplant. 2011 Jun;11(6):1201-1208. doi: 10.1111/j.1600-6143.2011.03518.x.

<http://www.ncbi.nlm.nih.gov/pubmed/21645253>

To prevent unintentional transmission of bloodborne pathogens through organ transplantation, organ procurement organizations (OPOs) screen potential donors by serologic testing to identify human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection. Newly acquired infection, however, may be undetectable by serologic testing. Our objective was to estimate the incidence of undetected infection among potential organ donors and to assess the significance of risk reductions conferred by nucleic acid testing (NAT) versus serology alone. We calculated prevalence of HIV and HCV-stratified by OPO risk designation-in 13 667 potential organ donors managed by 17 OPOs from 1/1/2004 to 7/1/2008. We calculated incidence of undetected infection using the incidence-window period approach. The prevalence of HIV was 0.10% for normal risk potential donors and 0.50% for high risk potential donors; HCV prevalence was 3.45% and 18.20%, respectively. For HIV, the estimated incidence of undetected infection by serologic screening was 1 in 50 000 for normal risk potential donors and 1 in 11 000 for high risk potential donors; for HCV, undetected incidence by serologic screening was 1 in 5000 and 1 in 1000, respectively. Projected estimates of undetected infection with NAT screening versus serology alone suggest that NAT screening could significantly reduce the rate of undetected HCV for all donor risk strata.

**Hepatitis C Virus Adversely Affects Quality of Life.** Cillo U, Amodio P, Ronco C, et al.

Blood Purif. 2011 Jun 10;32(2):144-149. [Epub ahead of print]

Soni SS, Zanus G, Minazzato L, Salari A, Neri D, Bombonato G, Schiff S, Bianco T.

<http://www.ncbi.nlm.nih.gov/pubmed/21659741>

**BACKGROUND:** Chronic liver disease secondary to hepatitis C virus (HCV) infection is a common clinical problem. HCV is likely to adversely affect the quality of life (QoL) of the patient. This effect is said to be disproportionate to the severity of the disease. The aim of our study was to evaluate QoL in HCV-positive patients focusing both on health status and subjective satisfaction. **METHODS:** Twenty-four patients with combined HCV and alcoholic liver disease (ETOH-HCV) were enrolled in the study. We adopted two generic tools: SF-36 (a health status questionnaire) and SAT-P (a satisfaction profile) for psychological assessment of the patients. SF-36 and SAT-P scores of ETOH-HCV patients were compared with scores of 23 patients with alcoholic liver disease (ETOH). The scores obtained from the study groups were also compared with the reference scores of the healthy Italian population. **RESULTS:** Both the groups were comparable with respect to age, histological and clinical severity of liver disease (as assessed by MELD and Child Pugh scores). Patients with ETOH-HCV scored less in the vitality and role emotional status domains of the SF-36 scores and the psychological function, social function and free time domains of the satisfaction profile. **CONCLUSIONS:** These results show a significant impact of HCV infection on health status and subjective satisfaction.

**Education by a Nurse Increases Response of Patients With Chronic Hepatitis C to Therapy With Peginterferon-alfa2a and Ribavirin.** Larrey D, Salse A, Ribard D, et al. Clin Gastroenterol Hepatol. 2011 Jun 6. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21683161>

**BACKGROUND & AIMS:** Education of patients with chronic hepatitis C has been proposed to increase response to therapy with peginterferon and ribavirin. We performed a prospective study to determine the effects of systematic consultation by a nurse on patient adherence and the efficacy of therapy. **METHODS:** We analyzed data from 244 patients who received either systematic consultation, after each medical visit, from a nurse who used a standard evaluation grid and provided information about the disease and treatment (group A [GrA], n= 123) or the conventional clinical follow-up procedure (group B [GrB], n = 121). Treatment lasted 24 to 48 weeks. **RESULTS:** Characteristics of each group were similar at baseline, including prior treatment (42.6% in GrA and 36.0% in GrB). Overall, GrA had significantly better adherence to treatment than GrB (74.0% vs 62.8%), especially among patients who received 48 weeks of treatment (69.7% vs 53.2%;  $P < .03$ ). Significantly more patients in GrA had a sustained virologic response, compared with GrB overall (38.2% vs 24.8%;  $P < .02$ ), as well as treatment-naive patients (47.1% vs 30.3%;  $P < .05$ ), and those with genotypes 1, 4, or 5 infections (31.6% vs 13.3%;  $P < .007$ ). There were no differences between GrA and GrB in response of patients with genotypes 2 or 3 infections or advanced fibrosis. Prognostic factors for a sustained virologic response (based on bivariate and multivariate analyses) were virologic response at week 12 (odds ratio [OR], 1.9;  $P < .0001$ ), genotypes 2 or 3 (OR, 2.9;  $P < .0001$ ), therapeutic education (OR, 2.5;  $P < .02$ ), and lack of previous treatment (OR, 2.3;  $P < .005$ ). **CONCLUSIONS:** Therapeutic education by a specialized nurse increases the response of patients with hepatitis C to therapy, particularly in difficult-to-treat patients.

**Clarification of interspousal hepatitis C virus infection in acute hepatitis C patients by molecular evolutionary analyses: Consideration on sexual and non-sexual transmission between spouses.** Nakamura I, Tanaka Y, Ochiai K, Moriyasu F, Mizokami M, Imawari M. Hepatol Res. 2011 Jun 23. doi: 10.1111/j.1872-034X.2011.00843.x. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21699638>

**AIM:** Previous studies evaluating the possibilities of interspousal sexual transmission of hepatitis C virus (HCV) have yielded many conflicting results. The aim of this study was to clarify the source of HCV infection in acute hepatitis C patients using phylogenetic analyses of nucleotide sequences of HCV E1 region. **METHODS:** Four acute hepatitis C patients were hospitalized in 2002-2007. The diagnosis was based on medical records, laboratory tests including HCV markers, and ultrasonographic examination of the liver. In each spouse of four patients, serum HCV antibody was assayed. In the subjects whose serum HCV antibody was positive, additional tests on HCV viral load and genotype were carried out. Then phylogenetic analyses of nucleotide sequences of partial HCV E1 region (440 nucleotides) of the patients and their spouses were performed. **RESULTS:** Hepatitis C virus antibody changed from negative to positive in the course of hospitalization and HCV RNA could be detected in every patient. Therefore they were diagnosed as acute hepatitis caused by HCV infection. In every spouse of four patients, HCV antibody and HCV RNA were positive. Three of four couples had the identical genotype and homogeneity of nucleotide sequences of HCV E1 region in three couples ranged from 97.9% to 100%. The results of phylogenetic analyses suggested that interspousal HCV infection occurred in the three couples. **CONCLUSION:** In conclusion, interspousal

infection might be one of the important sources of acute HCV infection in Japan. The usefulness of phylogenetic analysis of nucleotide sequences of HCV E1 region for clarifying interspousal HCV infection was validated.

**Directly acting antivirals against hepatitis C virus.** Soriano V, Vispo E, Poveda E, et al. J Antimicrob Chemother. 2011 Jun 7. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21652618>

The approval of directly acting antivirals (DAA) for the treatment of chronic hepatitis C virus (HCV) infection will represent a major breakthrough for the 180 million persons infected worldwide. Paradoxically, hepatitis C is the only human chronic viral disease that can be cured, as all other pathogenic viruses infecting humans either display self-limited courses or establish non-eradicated persistent infections. Until now, treatment of chronic hepatitis C consisted of the combination of peginterferon- $\alpha$  plus ribavirin, which provided limited rates of cure and was associated with frequent side effects. Several DAA have been identified that inhibit the NS3 protease, the NS5B polymerase or the NS5A replication complex, and have entered the final steps of clinical development. These molecules, coupled with significant progress made in the recognition of more potent and safe interferon forms (e.g. interferon- $\lambda$ ) and host protein targets (e.g. alisporivir), are opening a new era in hepatitis C therapeutics. The expectations are so great that, to some extent, it is reminiscent of what happened in 1996 in the HIV field when the introduction of the first protease inhibitors as part of triple combinations revolutionized antiretroviral therapy. To maximize treatment success and reduce the likelihood of drug resistance selection, a proper individualization of hepatitis C therapy will be required, choosing the most convenient drugs and strategies according to distinct viral and host profiles. The complexity of HCV therapeutics has reached a point that presumably will lead to the birth of a new specialist, the HCV doctor.

**Patient acceptance of universal screening for hepatitis C virus infection.** Coffin PO, Stevens AM, Scott JD, Stekler JD, Golden MR. BMC Infect Dis. 2011 Jun 6;11:160.

<http://www.ncbi.nlm.nih.gov/pubmed/21645388>

**BACKGROUND:** In the United States, about 70% of 2.9-3.7 million people with hepatitis C (HCV) are unaware of their infection. Although universal screening might be a cost-effective way to identify infections, prevent morbidity, and reduce transmission, few efforts have been made to determine patient opinions about new approaches to screening. **METHODS:** We surveyed 200 patients in August 2010 at five outpatient clinics of a major public urban medical center in Seattle, WA, with an 85.8% response rate. **RESULTS:** The sample was 55.3% women, median 47 years of age, and 56.3% white and 32.7% African or African-American; 9.5% and 2.5% reported testing positive for HCV and HIV, respectively. The vast majority of patients supported universal screening for HCV. When presented with three options for screening, 48% preferred universal testing without being informed that they were being tested or provided with negative results, 37% preferred testing with the chance to "opt-out" of being tested and without being provided with negative results, and 15% preferred testing based on clinician judgment. Results were similar for HIV screening. **CONCLUSIONS:** Patients support universal screening for HCV, even if that screening involves testing without prior consent or the routine provision of negative test results. Current screening guidelines and procedures should be reconsidered in light of patient priorities.

**Role of Lifestyle Changes in the Management of Chronic Liver Disease.** Nobili V, Carter-Kent C, Feldstein AE. BMC Med. 2011 Jun 6;9(1):70. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21645344>

The prevalence of obesity worldwide has dramatically increased during the last three decades. With obesity comes a variety of adverse health outcomes which are grouped under the umbrella of metabolic syndrome. The liver in particular seems to be significantly impacted by fat deposition in the presence of obesity. In this article we discuss several liver conditions which are directly affected by overweight and obese status, including nonalcoholic fatty liver disease, chronic infection with hepatitis C virus and post-liver transplant status. The deleterious effects of obesity on liver disease and overall health can be significantly impacted by a culture that fosters sustained nutritional improvement and regular physical activity. Here we summarize the current evidence supporting nonpharmacological, lifestyle interventions that lead to weight reduction, improved physical activity and better nutrition as part of the management and treatment of these liver conditions.

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## LIVER CANCER

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**Hepatitis C virus infection induces the expression of amphiregulin, a factor related to the activation of cellular survival pathways and required for efficient viral assembly.** Pei R, Chen H, Lu L, et al. J Gen Virol. 2011 Jun 8. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21653755>

Amphiregulin (AREG) is a ligand of epidermal growth factor (EGF) receptor and may play a role in development of cirrhosis and hepatocellular carcinoma in patients infected with hepatitis C virus (HCV). AREG showed an enhanced expression in HCV-infected human hepatoma cells according to gene array analysis. Therefore, we addressed the question about the role of AREG in HCV infection. AREG expression level was elevated in hepatoma cells containing a subgenomic HCV replicon or infected by HCV. Using a reporter assay, AREG promoter activity was found to be upregulated upon HCV infection. The enhanced AREG expression in hepatoma cells was partly caused by dsRNAs, HCV NS3 protein, and autocrine stimulation. AREG was able to activate cellular signaling pathways including ERK, Akt and p38, promote cell proliferation, and protect cells from HCV-induced cell death. Further, knockdown AREG expression increased the efficiency of HCV entry, as proven by HCVpp reporter assay. However, the formation and release of infectious HCV particles were reduced by AREG silencing with a concomitant accumulation of intracellular HCV RNA pool, indicating that the assembly and release of HCV progeny may require AREG expression. Blocking MAPK-ERK pathway by U0126 in Huh7.5.1 cells had the similar effect on HCV replication. In conclusion, HCV infection leads to an increase AREG expression in hepatocytes. AREG expression is essential for the efficient HCV assembly and virion release. Due to the activation of the cellular survival pathways, AREG may counteract HCV-induced apoptosis of infected hepatocytes and facilitate the development of liver cirrhosis and hepatocellular carcinoma.

**Amino acid substitutions in hepatitis C virus core region predict hepatocarcinogenesis following eradication of HCV RNA by antiviral therapy.** Akuta N, Suzuki F, Hirakawa M, et al. J Med Virol. 2011 Jun;83(6):1016-22. doi: 10.1002/jmv.22094.

<http://www.ncbi.nlm.nih.gov/pubmed/21503914>

Substitution of amino acid (aa) 70 and/or 91 in the core region of HCV genotype 1b (HCV-1b) is an important predictor of hepatocarcinogenesis, but its impact on the development of hepatocellular carcinoma (HCC) following eradication of HCV RNA by antiviral therapy is not clear. 1,273 patients with HCV-related chronic liver disease, with sustained virological response, defined as negative HCV RNA at 24 weeks after cessation of interferon monotherapy or interferon plus ribavirin combination therapy, were included in a follow-up study to evaluate the impact of aa substitution in the core region on hepatocarcinogenesis. Twenty six patients developed HCC during the follow-up. The cumulative rates of new HCC were 3.2%, 4.8%, and 8.6% at the end of 5, 10, and 15 years, respectively. The rates in patients infected with HCV-1b/Gln70(His70) [glutamine (histidine) at aa 70] were significantly higher than in patients infected with HCV-1b/Arg70 (arginine at aa 70) ( $P = 0.007$ ; log-rank test) and HCV-2a/2b ( $P < 0.001$ ; log-rank test). The rates in patients infected with HCV-1b/Arg70 were not significantly higher than in those infected with HCV-2a/2b ( $P = 0.617$ ; log-rank test). Multivariate analysis identified HCV-1b/Gln70(His70) (HR 10.5,  $P < 0.001$ ), advanced fibrosis (HR 9.03,  $P = 0.002$ ), and old age (HR 3.09,  $P = 0.066$ ) as determinants of hepatocarcinogenesis. **In conclusion**, aa substitution in the core region of HCV-1b at the start of antiviral therapy is an important predictor of HCC following eradication of HCV RNA. This study emphasizes the importance of detection of aa substitutions in the core region before antiviral therapy.

**Hepatocellular nodules in liver cirrhosis: MR evaluation.** Lee JM, Choi BI. *Abdom Imaging*. 2011 Jun;36(3):282-9.

<http://www.ncbi.nlm.nih.gov/pubmed/21399975>

Liver cirrhosis is a major public health problem worldwide. Common causes of cirrhosis include hepatitis C virus, hepatitis B virus, alcohol consumption, and nonalcoholic steatohepatitis. Cirrhotic livers are characterized by advanced hepatic fibrosis and the development of hepatocellular nodules such as regenerative nodules, dysplastic or neoplastic nodules. Cirrhosis is the strongest predisposing factor for hepatocellular carcinoma (HCC). For example, viral hepatitis is the main risk factor for cirrhosis and is associated with the increased incidence (1%-4% per year) of HCC after development of cirrhosis. Currently, a variety of imaging modalities, including ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and positron-emission tomography (PET) are used in noninvasive evaluation of patients with chronic liver disease and suspected HCC. With technological development of MR scanners, MR imaging has emerged as an important imaging modality for assessing cirrhosis and its complications such as HCC. The recent advance in MR is the introduction of faster sequences which have allowed high-quality imaging of the entire liver with high intrinsic soft-tissue contrast, and also multiphasic dynamic MRI that is essential for the detection and characterization of HCC. In addition, functional MRI including diffusion-weighted MRI, MR elastography, and new MR contrast agent with dual function have been investigated for the clinical utility of detection and characterization of HCCs. In this article, we provide an overview of the state-of-the-art MR imaging techniques being used for noninvasive assessment of hepatocellular nodules including conventional dynamic imaging, liver-specific contrast-enhanced MR imaging, diffusion-weighted imaging, MR spectroscopy, and MR elastography.

**Rising incidence and demographics of hepatocellular carcinoma in the USA: what does it mean?** Shaw JJ, Shah SA. *Expert Rev Gastroenterol Hepatol.* 2011 Jun;5(3):365-70.

<http://www.ncbi.nlm.nih.gov/pubmed/21651354>

The incidence of hepatocellular carcinoma (HCC) is increasing in the USA. Traditional factors, such as hepatitis C and hepatitis B, along with new emerging trends suggest that the incidence is not only increasing, but is also likely to be under-represented in the current literature. Emerging knowledge of its incidence and epidemiology reflects an increased incidence in younger patients and certain ethnic groups. Without a clear treatment algorithm for this complex cancer, therapy and its utilization remain unclear.

**Impact of Pegylated Interferon Therapy on Outcomes of Patients with Hepatitis C Virus-Related Hepatocellular Carcinoma After Curative Hepatic Resection.** Tanimoto Y, Tashiro H, Aikata H, et al. *Ann Surg Oncol.* 2011 Jun 28. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21710324>

**BACKGROUND:** Several published reports investigating the effects of interferon (IFN) therapy on survival and tumor recurrence after curative resection of hepatocellular carcinoma (HCC) have been inconclusive. The aim of this study is to investigate the efficacy of pegylated-IFN (peg-IFN) therapy after curative hepatic resection for HCC in patients infected with hepatitis C virus (HCV). **METHODS:** Data from 175 patients who underwent curative hepatic resection for HCC associated with HCV were retrospectively collected and analyzed; 75 patients received peg-IFN therapy after surgery, whereas 100 patients did not receive IFN therapy. To overcome biases resulting from the different distribution of covariates in the two groups, a one-to-one match was created using propensity score analysis. After matching, patient outcomes were analyzed. **RESULTS:** After one-to-one matching, patients (n = 38) who received peg-IFN therapy after surgery and patients (n = 38) who did not receive IFN therapy had the same preoperative and operative characteristics. The 3- and 5-year overall survival rates of patients who received peg-IFN therapy after hepatic resection were significantly higher than those of patients who did not receive IFN therapy (P = 0.00135). The 3- and 5-year overall survival rates were 100 and 91.7% and 76.6 and 50.6% in the peg-IFN group and non-IFN group, respectively. There was no significant difference in disease-free survival between the two matched groups (P = 0.886). **CONCLUSION:** Peg-IFN therapy may be effective as an adjuvant chemopreventive agent after hepatic resection in patients with HCV-related HCC.

**Serum levels of  $\beta$ -catenin as a potential marker for genotype 4/hepatitis C-associated hepatocellular carcinoma.** Zekri AR, Bahnassy AA, Alam El-Din HM, et al. *Oncol Rep.* 2011 Jun 21. doi: 10.3892/or.2011.1355. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/21701780>

The global rising incidence of hepatocellular carcinoma (HCC), which parallels the increase of hepatitis C virus (HCV) prevalence, has sparked a renewed interest in discovering additional HCC serum markers. In this study, we investigated the clinical use of serum E-cadherin, ICAM, MMP-2, VEGF, OPN and  $\beta$ -catenin as potential diagnostic makers for HCV/genotype 4-associated HCC. Twenty cases of healthy subjects, 11 cases with asymptomatic HCV/genotype 4 carriers (ASC), 28 chronic hepatitis (CH) cases and 32 patients with HCC were enrolled in this study. Serum levels of proteins were measured by a sandwich-enzyme-linked (ELISA) assay. The diagnostic accuracy of each candidate marker was evaluated using receiver-operating characteristic (ROC) curve analysis, reporting the area under the curve (AUC) and its 95%

confidence interval (CI). We demonstrated that serum  $\beta$ -catenin levels were significantly elevated in patients with HCC compared to those with CH, ASC and healthy controls. Among the six studied markers,  $\beta$ -catenin was also found to be the only marker that can significantly discriminate between patients with HCC and those with CH; therefore,  $\beta$ -catenin could be considered as a potential marker for early diagnosis of HCV-associated HCC in patients infected with HCV genotype 4.

**Diagnostic significance of plasma osteopontin in hepatitis C virus-related hepatocellular carcinoma.** Abu El Makarem MA, Abdel-Aleem A, Ali A, Saber R, et al. Ann Hepatol. 2011 Jun 1;10(3):296-305.

<http://www.ncbi.nlm.nih.gov/pubmed/21677331>

**BACKGROUND AND AIM:** Outcome of hepatocellular carcinoma (HCC) depends mainly on its early diagnosis. The performance of traditional biomarkers is not satisfactory. Osteopontin (OPN) is of potential importance. This study aim to assess the diagnostic value of plasma OPN compared with alpha-fetoprotein (AFP) for the diagnosis of HCV- related HCC. **METHODS:** We recruited 113 HCC patients compared with 120 matched cirrhotic patients and 120 Controls. The plasma level of OPN and serum AFP for all participants were assessed. **RESULTS:** The median plasma OPN level was significantly higher in the HCC group than in the cirrhotic patient group or in the normal control group (p-value < 0.001), while OPN levels were not differed significantly in correlation with the degree of liver function deterioration in terms of advanced Child-Pugh class (p-value < 0.9). The diagnostic efficacy of OPN were superior to AFP in terms of AUC, sensitivity, specificity, PPV and NPV either in diagnosis of early or late stages of HCC (0.88 vs. 0.56; P = 0.0001, 0.991vs. 0.899; p = 0.01; respectively). **CONCLUSION:** Plasma OPN level is a potential diagnostic marker for HCC, especially among high-risk group of patients. These values extend beyond the traditional tumor biomarkers as AFP, as it possesses good prognostic value.