



Caring Ambassadors Hepatitis C Program Newsletter

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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naïve patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. Kwo PY, Lawitz EJ, McCone J, et al. *Lancet*. 2010 Aug 28;376(9742):705-716. Epub 2010 Aug 6.

<http://www.ncbi.nlm.nih.gov/pubmed/20692693>

BACKGROUND: Peginterferon plus ribavirin achieves sustained virological response (SVR) in fewer than half of patients with genotype 1 chronic hepatitis C virus infection treated for 48 weeks. We tested the efficacy of boceprevir, an NS3 hepatitis C virus oral protease inhibitor, when added to peginterferon alfa-2b and ribavirin. **METHODS:** In part 1 of this trial, undertaken in 67 sites in the USA, Canada, and Europe, 520 treatment-naïve patients with genotype 1 hepatitis C virus infection were randomly assigned to receive peginterferon alfa-2b 1.5 µg/kg plus ribavirin 800-1400 mg daily for 48 weeks (PR48; n=104); peginterferon alfa-2b and ribavirin daily for 4 weeks, followed by peginterferon alfa-2b, ribavirin, and boceprevir 800 mg three times a day for 24 weeks (PR4/PRB24; n=103) or 44 weeks (PR4/PRB44; n=103); or peginterferon alfa-2b, ribavirin, and boceprevir three times a day for 28 weeks (PRB28; n=107) or 48 weeks (PRB48; n=103). In part 2, 75 patients were randomly assigned to receive either PRB48 (n=16) or low-dose ribavirin (400-1000 mg) plus peginterferon alfa-2b and boceprevir three times a day for 48 weeks (low-dose PRB48; n=59). Randomisation was by computer-generated code, and study personnel and patients were not masked to group assignment. The primary endpoint was SVR 24 weeks after treatment. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00423670. **FINDINGS:** Patients in all four boceprevir groups had higher rates of SVR than did the control group (58/107 [54%, 95% CI 44-64], p=0.013 for PRB28; 58/103 [56%, 44-66], p=0.005 for PR4/PRB24; 69/103 [67%, 57-76], p<0.0001 for PRB48; and 77/103 [75%, 65-83], p<0.0001 for PR4/PRB44; vs 39/104 [38%, 28-48] for PR48 control). Low-dose ribavirin was associated with a high rate of viral breakthrough (16/59 [27%]), and a rate of relapse (six of 27 [22%]) similar to control (12/51 [24%]). Boceprevir-based groups had higher rates of anaemia (227/416 [55%] vs 35/104 [34%]) and dysgeusia (111/416 [27%] vs nine of 104 [9%]) than did the control group.

INTERPRETATION: In patients with untreated genotype 1 chronic hepatitis C infection, the addition of the direct-acting antiviral agent boceprevir to standard treatment with peginterferon and ribavirin after a 4-week lead-in seems to have the potential to double the sustained response rate compared with that recorded with standard treatment alone.

Is chronic hepatitis C virus infection a risk factor for breast cancer? Larrey D, Bozonnat MC, Kain I, Pageaux GP, Assenat E. World J Gastroenterol. 2010 Aug 7;16(29):3687-91. <http://www.ncbi.nlm.nih.gov/pubmed/20677341>

AIM: To evaluate the prevalence of breast tumors in adult females with chronic hepatitis C virus (HCV) infection. **METHODS:** Prospective, single-center study, based on female outpatients consulting in a liver unit, for 1 year. The study group included females with present and/or past history of chronic infection by HCV. Patients with spontaneous recovery were excluded. Chronic hepatitis had been proved by liver biopsy in the majority of cases and/or biological markers of inflammation and fibrosis. The control group included female patients with other well documented chronic liver diseases: chronic hepatitis B, alcoholic liver disease, autoimmune hepatitis, hemochromatosis, non alcoholic liver disease, chronic cholangitis. Participating patients were prospectively questioned during consultation about past breast history and follow-up by mammography. **RESULTS:** Breast carcinoma was recorded in 17/294 patients with HCV infection (5.8%, 95% CI: 3.1-8.4) vs 5/107 control patients (4.7%, 95% CI: 0.67-8.67). Benign tumors of the breast (mastosis, nodules, cysts) were recorded in 75/294 patients with HCV infection (25.5%, 95% CI: 20.5-30.5) vs 21/107 (19.6%, 95% CI: 12.1-27.1) in the control group. No lesion was noted in 202 patients with HCV (68.7%, 95% CI: 63.4-74) vs 81 control patients (75.7%, 95% CI: 67.6-83.8). Despite a trend to an increased prevalence in the group with HCV infection, the difference was not significant compared to the control group (P = NS). In patients over 40 years, the results were, respectively, as follows: breast cancer associated with HCV: 17/266 patients (6.3%, 95% CI: 3.4-9.3) vs 5/95 patients (5.2%, 95% CI: 0.7-9.7) in the control group; benign breast tumors: 72/266 patients with HCV infection (27%, 95% CI: 21.7-32.4) vs 18/95 patients (18.9%, 95% CI: 11-26.8) in the control group; no breast lesion 177/266 (66.5%, 95% CI: 60.9-72.2) in patients with HCV infection vs 72/95 (75.7%, 95% CI: 67.1-84.4) in the control group. The differences were not significant (P = NS). **CONCLUSION:** These results suggest that chronic HCV infection is not a strong promoter of breast carcinoma in adult females of any age.

Alpha-fetoprotein above normal levels as a risk factor for the development of hepatocellular carcinoma in patients infected with hepatitis C virus. Tateyama M, Yatsushashi H, Taura N, et al. J Gastroenterol. 2010 Aug 14. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/20711614>

BACKGROUND: Noninvasive risk factors are required for predicting the development of hepatocellular carcinoma (HCC) not only in patients with cirrhosis but also in those with chronic hepatitis who are infected with hepatitis C virus (HCV). **METHODS:** A total of 707 patients with chronic HCV infection without other risks were evaluated for the predictive value of noninvasive risk factors for HCC, including age, sex, viral load, genotype, fibrosis stage, aspartate and alanine aminotransferase levels, bilirubin, albumin, platelet count, and alpha-fetoprotein (AFP) at entry to the study, as well as interferon (IFN) therapy they received. **RESULTS:** The ten-year cumulative incidence rates of HCC for patients with fibrosis stages F0/F1, F2, F3, and F4 were 2.5, 12.8, 19.3, and 55.9%, respectively. Multivariate analysis identified age ≥ 57 years [hazard ratio (HR) 2.026, P = 0.004], fibrosis stage F4 (HR 3.957, P < 0.001), and AFP 6-20 ng/mL (HR 1.942, P = 0.030) and ≥ 20 ng/mL (HR 3.884, P < 0.001), as well as the response to IFN [relative risk (RR) 0.099, P < 0.001], as independent risk factors for the development of HCC. The ten-year cumulative incidence rates of HCC in the patients with AFP levels of <6, 6-20, and ≥ 20 ng/mL at entry were 6.0, 24.6, and 47.3%, respectively.

CONCLUSIONS: Not only high (>20 ng/mL), but also even slightly elevated (6-20 ng/mL) AFP levels, could serve as a risk factor for HCC to complement the fibrosis stage. In contrast, AFP levels <6 ng/mL indicate a low risk of HCC development in patients infected with HCV, irrespective of the fibrosis stage.

Quality of care in patients with chronic hepatitis C virus infection: a cohort study.

Kanwal F, Schnitzler MS, Bacon BR, et al. *Ann Intern Med.* 2010 Aug 17;153(4):231-9.

<http://www.ncbi.nlm.nih.gov/pubmed/20713791>

BACKGROUND: Medicare has proposed quality-of-care indicators for chronic hepatitis C virus (HCV) infection. The extent to which these standards are met in practice is largely unknown. **OBJECTIVE:** To evaluate the quality of health care that patients with HCV receive and the factors associated with receipt of quality care. **DESIGN:** Retrospective cohort study. **SETTING:** Nationwide U.S. health insurance company research database. **PARTICIPANTS:** 10 385 patients with HCV enrolled in the database between 2003 and 2006. Patients were included if they were eligible for at least 1 quality indicator. **MEASUREMENTS:** Quality of HCV care received by patients, as measured by 7 explicit quality indicators included in Medicare's 2009 Physician Quality Reporting Initiative. **RESULTS:** Proportions of patients meeting quality indicators varied, ranging from 21.5% for vaccination to 79% for the HCV genotype testing indicator. Overall, 18.5% of patients (95% CI, 18% to 19%) received all recommended care. Older age and presence of comorbid conditions were associated with lower quality, whereas elevated liver enzyme levels, cirrhosis, and HIV infection were associated with higher quality. Patients who saw both generalists and specialists received the best care (odds ratio of receiving care for which a patient is eligible: specialists alone, 0.79 [CI, 0.66 to 0.95]; primary care physician alone, 0.44 [CI, 0.40 to 0.48]). **LIMITATIONS:** The study had an observational retrospective design, used a convenience sample, and had no information on patient ethnicity. It may be that the indicators or the reporting of the indicators of HCV care--and not the care itself--is suboptimum. **CONCLUSION:** Health care quality, based on Medicare criteria, is suboptimum for HCV. Care that included both specialists and generalists is associated with the best quality. Our results support the development of specialist and primary care collaboration to improve the quality of HCV care.

HCV treatment-related anemia is associated with higher sustained virologic response rate.

Sulkowski MS, Shiffman ML, Afdhal NH, et al. *Gastroenterology.* 2010 Aug 16. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20723545>

BACKGROUND & AIMS: Hepatitis C virus (HCV) treatment is frequently complicated by anemia from ribavirin (RBV)-related hemolysis and peginterferon-alfa (PEG-IFN)- related bone marrow suppression. We investigated the relationships among treatment outcomes, anemia, and its management with RBV dose reduction and/or erythropoiesis-stimulating agents (ESAs). **METHODS:** We analyzed data from a trial conducted at 118 United States academic and community centers in treatment-naïve patients with HCV genotype 1. Patients were treated for as many as 48 weeks with 1 of 3 PEG-IFN/RBV regimens. ESAs were given to anemic patients (Hb <10 g/dL) after RBV dose reduction. Sustained virologic responses (SVR) were assessed based on decreases in Hb, anemia, and ESA use. **RESULTS:** While patients received treatment, 3023 had their Hb levels measured at least once. A SVR was associated with the magnitude of Hb decrease: >3 g/dL, 43.7%; <=3 g/dL, 29.9% (P <0.001). Anemia occurred in 865 patients

(28.6%); 449 of these (51.9%) used ESAs. In patients with early-onset anemia (≤ 8 weeks of treatment), ESAs were associated with higher SVR rate (45.0% > 25.9%; $P < 0.001$) and reduced discontinuation of treatment because of adverse events (12.6% < 30.1%, $P < 0.001$). ESAs did not affect SVR or discontinuation rates among patients with late-stage anemia. **CONCLUSION:** Among HCV genotype 1-infected patients treated with PEG-IFN/RBV, anemia was associated with higher rates of SVR. The effect of ESAs varied by time to anemia; patients with early-onset anemia had higher rates of SVR with ESA use whereas no effect was observed in those with late-onset anemia. Prospective trials are needed to assess the role of ESAs in HCV treatment.

Effects of recognizing depression with a standardized questionnaire (CES-D) versus patient reporting of depression after a single-standardized question on the outcomes of treatment for hepatitis C with pegylated interferon-alpha-2b and ribavirin. Phillips FH, Prebis M, Grumbeck C, et al. Eur J Gastroenterol Hepatol. 2010 Aug 26. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/20802340>

BACKGROUND: Depression may worsen during antiviral treatment for hepatitis C virus, resulting in noncompliance treatment. **AIM:** The aim was to compare the response and compliance rates between the groups of veteran patients using two different methods of identifying depression, either the Centers for Epidemiology Studies for Depression Scale (group A) questionnaire or the report of symptoms of depression after a single-standardized question by the health care provider (group B). **METHODS:** One hundred and twenty-nine patients were randomly assigned to the two groups before the treatment. **RESULTS:** No statistical differences were noted in baseline characteristics between the groups. Depression was common in both the groups. No difference between initial Centers for Epidemiologic Studies Depression Scale scores and diagnosis of depression between the two groups was noted. Furthermore, the number of patients diagnosed with depression during the treatment was similar in each group. There were no significant differences between the groups in rates of sustained viral response (30% group A, 35% group B) or in rates of overall compliance with patients receiving more than 90% of prescribed PegIntronA therapy (44% group A, 39% group B), and ribavirin (32% group A and 37% group B). **CONCLUSION:** The use of the Centers for Epidemiology Studies for Depression Scale questionnaire to recognize depression had no significant advantage over patient reporting of depression symptoms after a single-standardized question on the hepatitis C virus clearance and the treatment compliance rates in veteran populations.

Treatment of chronic hepatitis C using a 4-week lead-in with nitazoxanide before peginterferon plus nitazoxanide. Rossignol JF, Elfert A, Keeffe EB. J Clin Gastroenterol. 2010 Aug;44(7):504-9.

<http://www.ncbi.nlm.nih.gov/pubmed/20048684>

GOALS: The primary aim of this study was to further evaluate the efficacy of peginterferon plus nitazoxanide without ribavirin using a 4-week lead-in. **BACKGROUND:** The initial treatment of chronic hepatitis C with nitazoxanide used 12 weeks of nitazoxanide monotherapy before combination therapy with peginterferon with or without ribavirin. **STUDY:** This open-label pilot study enrolled 44 treatment-naive patients with chronic hepatitis C (40 with genotype 4; 3 with genotype 1; and 1 with genotype 2). The patients received oral nitazoxanide 500 mg twice daily for 4 weeks followed by nitazoxanide plus peginterferon alfa-2a 180 mug weekly for 36 weeks and were then followed for 24 weeks. The results of this study were compared with those from an overlapping historical trial using 12 weeks of nitazoxanide lead-in. **RESULTS:** A sustained

virologic response (SVR) was achieved in 80% of patients, which was similar to the SVR rates in the historical trial, that is, 79% and 61% in patients treated with and without ribavirin, respectively. A rapid virologic response occurred in 59% of patients, which was also similar to the rapid virologic response rates in the historical trial (64% and 54% in patients treated with and without ribavirin, respectively). All 4 patients with genotypes 1 and 2 had an SVR.

CONCLUSIONS: The nitazoxanide lead-in phase before combination therapy with peginterferon can likely be reduced from 12 weeks to 4 weeks without compromising virologic response rates. In addition, treatment of chronic hepatitis C with peginterferon plus nitazoxanide without ribavirin is promising and requires further study.

Prevalence and impact of manic traits in depressed patients initiating interferon therapy for chronic hepatitis C infection. Lim C, Olson J, Zaman A, Phelps J, Ingram KD. J Clin Gastroenterol. 2010 Aug;44(7):e141-6.

<http://www.ncbi.nlm.nih.gov/pubmed/20495465>

GOALS: To evaluate the impact of manic traits on adverse events in depressed hepatitis C patients initiating interferon therapy. **BACKGROUND:** Interferon alpha therapy for hepatitis C can exacerbate preexisting depression. Bipolar disorder frequently presents as depressive symptoms that are indistinguishable from or misdiagnosed as major depressive disorder. The impact of bipolar disorder on adverse psychiatric events during therapy is unknown. **STUDY:** A retrospective study was performed on consecutive patients initiating interferon therapy in the Hepatology clinic at a tertiary-care center between December 2004 and October 2007. All patients completed the Physicians Health Questionnaire (PHQ-9), a validated survey for major depressive disorder. Patients with a positive PHQ screen completed the Mood Disorders Questionnaire (MDQ), a validated screening tool for manic traits. Patients with a negative PHQ served as controls. All adverse psychiatric events were documented through retrospective record review for 6 months after interferon initiation. **RESULTS:** A total of 165 patients were treated with interferon alpha. One hundred thirty-two (80%) had a negative PHQ (controls) and 33 had a positive PHQ. Forty-one (30%) of the control patients had adverse psychiatric events. Psychiatric events occurred in 8 of 22 (36%) patients with positive PHQ but negative MDQ; 8 of 11 (73%) with positive PHQ and positive MDQ had psychiatric adverse events. This finding was statistically significant compared with the control group ($P=0.007$). The overall sustained viral response rate was 58% and was not statistically significant among groups. **CONCLUSIONS:** Baseline manic traits, as detected by the MDQ, were associated with high rates of adverse psychiatric events among individuals receiving antiviral therapy.

Influence of body mass index on outcome of pediatric chronic hepatitis C virus infection. Delgado-Borrego A, Healey D, Negre B, et al. J Pediatr Gastroenterol Nutr. 2010 Aug;51(2):191-7.

<http://www.ncbi.nlm.nih.gov/pubmed/20531022>

BACKGROUND AND AIMS: Evidence demonstrates that obesity is associated with progression of chronic hepatitis C virus (HCV) infection and poor response to interferon therapy among HCV-infected adults. However, this evidence has been confounded by multiple comorbidities present in adult cohorts and the use of single adult doses. **PATIENTS AND METHODS:** We performed a retrospective investigation to evaluate the role of body mass index (BMI) in chronic HCV progression and response to therapy in the children. One hundred twenty-three children and teenagers studied at Children's Hospital Boston for HCV infection between

1998 and 2007 were included. Patients' weight and height at the time of liver biopsy or before and after HCV therapy were obtained and BMI was calculated. **RESULTS:** The presence of steatosis was statistically associated with higher mean (+/-SE) BMI percentiles (72nd +/- 5.8 vs 58th +/- 3.5) percentile; $F(1,101) = 4.2, P = 0.04$. Nonresponders to treatment had a higher mean (+/-SE) BMI percentile (70th +/- 7.4) when compared with responders (50th +/- 6.5) in univariate and multivariate analyses ($P = 0.04, P = 0.02$, respectively). Using a multivariate model, it was calculated that 1 standard deviation (1 z-score unit) increase in baseline BMI z score is associated with a 12% decrease in the probability of sustained virologic response. **CONCLUSIONS:** Overweight adversely affects the progression of chronic HCV liver disease and is associated with diminished response to antiviral therapy using weight-based dosing in a cohort with minimal comorbidities.

Ophthalmologic complications in children with chronic hepatitis C treated with pegylated interferon. Narkewicz MR, Rosenthal P, Schwarz KB, et al. *J Pediatr Gastroenterol Nutr.* 2010 Aug;51(2):183-6.

<http://www.ncbi.nlm.nih.gov/pubmed/20512062>

OBJECTIVES: Interferon treatment for chronic viral hepatitis C (HCV) has been associated with the development of retinopathy in 19% to 29% of adults. Our purpose is to describe the ophthalmologic complications of pegylated interferon-alpha2a with either placebo or ribavirin in children with chronic HCV (the PEDS-C trial). **MATERIALS AND METHODS:** Prospective, comprehensive ophthalmologic examinations including slit lamp at enrollment and after 24 and 48 weeks of treatment of 114 children participating in a randomized clinical trial. **RESULTS:** One hundred and twenty-eight children were screened for entry, of whom 123 had an eye examination and no child had existing retinal disease. One hundred fourteen children were eligible and were treated. One hundred ten children had an eye examination at 24 weeks and 103 children at 48 weeks. Three of 114 subjects (2.6%) developed documented ($n = 2$) or possible (1) serious eye complications. One subject developed evidence of ischemic retinopathy (cotton-wool spots) by week 24, 1 developed uveitis by week 48, and 1 reported at week 48 transient (<4 hours) monocular blindness that had occurred at week 36 with a subsequent normal examination at week 48. **CONCLUSIONS:** Ophthalmologic complications are infrequent in children who are treated with pegylated interferon-alpha2a for HCV (2%-3%). Because of the potential severity of ischemic retinopathy and uveitis, prospective ocular assessment should remain part of the monitoring strategy for children who are treated with interferon for HCV.

Re-treatment of children with chronic hepatitis C who did not respond to interferon-alpha treatment. Gerner P, Hilbich J, Wenzl TG, et al. *J Pediatr Gastroenterol Nutr.* 2010 Aug;51(2):187-90.

<http://www.ncbi.nlm.nih.gov/pubmed/20512050>

BACKGROUND: Many patients with chronic hepatitis C do not respond to antiviral treatment. In adult patients the re-treatment of these patients has been extensively investigated. Because the response to re-treatment in children is not well defined we evaluated the efficacy and safety of interferon (IFN)-alpha plus ribavirin in patients who have failed to respond to previous treatment. **PATIENTS AND METHODS:** In an open-label, uncontrolled study, 18 chronically infected children were investigated. Fifteen children had been treated with IFN-alpha plus ribavirin and 3 patients with IFN-alpha alone. Fourteen patients were nonresponders; 4 experienced viral breakthrough during treatment and/or relapse after treatment. Patients received

IFN-alpha 3 times per week subcutaneously plus ribavirin for 48 weeks. Sixteen patients were infected with hepatitis C virus (HCV) genotype 1, 2 with genotype 4, and 1 with genotype 3 and co-infection with hepatitis B. **RESULTS:** Four patients showed early viral response to therapy and became HCV-RNA negative after 12 weeks. Sustained viral response (HCV-RNA negative 6 months after end of treatment) was documented in 2 of them. These 2 patients belonged to the group of 4 children who relapsed or experienced a viral breakthrough during previous treatment. None of the 14 patients with prior nonresponse had sustained viral response. **CONCLUSIONS:** Re-treatment with IFN-alpha plus ribavirin may be useful in children who relapsed in a previous antiviral treatment but seems not to be useful in nonresponders. These results are in line with studies from adult patients and should be therefore encouraged to provide a second chance for healing in a subgroup of patients.

Safety and immunogenicity of HCV E1E2 vaccine adjuvanted with MF59 administered to healthy adults. Frey SE, Houghton M, Coates S, et al. Vaccine. 2010 Aug 31;28(38):6367-73. Epub 2010 Jul 7.

<http://www.ncbi.nlm.nih.gov/pubmed/20619382>

BACKGROUND: Hepatitis C virus (HCV) causes chronic liver disease that often leads to cirrhosis and hepatocellular carcinoma. In animal studies, chimpanzees were protected against chronic infection following experimental challenge with either homologous or heterologous HCV genotype 1a strains which predominate in the USA and Canada. We describe the first in humans clinical trial of this prophylactic HCV vaccine. **METHODS:** HCV E1E2 adjuvanted with MF59C.1 (an oil-in-water emulsion) was given at 3 different dosages on day 0 and weeks 4, 24 and 48 in a phase 1, placebo-controlled, dose escalation trial to healthy HCV-negative adults. **RESULTS:** There was no significant difference in the proportion of subjects reporting adverse events across the groups. Following vaccination subjects developed antibodies detectable by ELISA, CD81 neutralization and VSV/HCV pseudotype neutralization. There were no significant differences between vaccine groups in the number of responders and geometric mean titers for each of the three assays. All subjects developed lymphocyte proliferation responses to E1E2 and an inverse response to increasing amounts of antigen was noted. **CONCLUSIONS:** The vaccine was safe and generally well-tolerated at each of the 3 dosage levels and induced antibody and lymphoproliferative responses. A larger study to further evaluate safety and immunogenicity is warranted.

Preclinical and clinical development of pegylated interferon-lambda 1 in chronic hepatitis C. Ramos EL. J Interferon Cytokine Res. 2010 Aug;30(8):591-5.

<http://www.ncbi.nlm.nih.gov/pubmed/20645873>

Current treatment of chronic hepatitis C consists of pegylated interferon-alpha (PEG-IFN-alpha) in combination with ribavirin. This regimen is associated with adverse effects that can limit its use. PEG-IFN-lambda 1 (pegIFNlambda) is a novel IFN that shares many of the biological effects of IFN-alpha but may have fewer side effects due to its more selective receptor distribution. Preclinical data show that pegIFNlambda has antiviral activity against hepatitis C virus (HCV) but does not inhibit myeloid colony formation. A phase 1 study in healthy volunteers demonstrated that pegIFNlambda is well tolerated. Elevated liver enzymes resulted in a dose-limiting toxicity after a single dose of 7.5 microg/kg, the highest dose tested. A phase 1b study in genotype 1 HCV patients who either relapsed after IFN-alpha therapy or naive to therapy was initiated. Interim data from the treatment relapse subset showed viral load reductions

of 2.3 to 4.0 logs when pegIFNlambda was administered weekly as a single agent with or without ribavirin for up to 4 weeks. Drug-related side effects included elevation of liver enzymes. Decreases in hemoglobin were observed only in patients receiving ribavirin. Constitutional symptoms appeared lower than historical data for PEG-IFN-alpha. **These results form** the basis of further development of pegIFNlambda as a novel treatment for chronic hepatitis C.

The interferon stimulated gene 15 functions as a proviral factor for the hepatitis C virus and as a regulator of the IFN response. Broering R, Zhang X, Kottlilil S, et al. Gut. 2010 Aug;59(8):1111-9.

<http://www.ncbi.nlm.nih.gov/pubmed/20639253>

BACKGROUND: Non-response to combination therapy by patients with hepatitis C virus (HCV) has previously been associated with a strong hepatic upregulation of interferon stimulated genes (ISGs) including ISG15. Therefore, the aim of this study was to further elucidate the functional role of this molecule. **METHODS:** ISG15 expression was suppressed by siRNAs or enhanced by over-expression in genomic and subgenomic human or murine HCV replicon systems. In addition, ISG15 expression was analysed in liver samples of patients with HCV prior to antiviral therapy and correlated with clinical and virological parameters. **RESULTS:** Short- or long-term knockdown of ISG15 expression suppressed HCV replication comparable to IFNs without evidence for the induction of resistant mutations. Triple therapy consisting of ISG15 knockdown, interferon alpha (IFNalpha) and ribavirin led to complete suppression of the HCV NS5A protein, corresponding to 99% suppression of HCV-RNA compared to 75% suppression by IFNalpha and ribavirin only. Combination treatment of ISG15 knockdown and IFN was associated with enhanced and prolonged expression of selected ISGs. Consistent with these in vitro data, high hepatic ISG15 levels correlated with the unfavourable HCV genotype 1, a high hepatic HCV load and a low antiviral response to IFN during the initial phase of treatment. **CONCLUSIONS:** ISG15 plays an important role in the HCV replication cycle. Therefore, therapies based on the suppression of ISG15 may provide a promising strategy to overcome non-response to standard combination treatment in the future. Furthermore, analysis of ISG15 prior to therapy may be useful to predict short-term and long-term outcome and thus tailor antiviral therapy with pegIFN and ribavirin.

New NS5B polymerase inhibitors for hepatitis C. Legrand-Abravanel F, Nicot F, Izopet J. Expert Opin Investig Drugs. 2010 Aug;19(8):963-75.

<http://www.ncbi.nlm.nih.gov/pubmed/20629614>

IMPORTANCE OF THE FIELD: The current treatment of chronic hepatitis C based on the combination of pegylated interferon and ribavirin is effective in only 50% of patients. Specific targeted antiviral therapies represent a promising approach to eradicate the infection. **AREAS COVERED IN THIS REVIEW:** This review focuses on progress towards the development of the hepatitis C virus (HCV) polymerase inhibitors that have entered clinical development in recent years. **WHAT THE READER WILL GAIN:** Nucleos(t)ide analogues target the active site of the HCV polymerase and acts as chain terminators. They have similar activity against all genotypes and the virus has a high genetic barrier to drug resistance. Non-nucleoside inhibitors achieve polymerase inhibition by binding to one of the at least four allosteric enzyme sites. Most of them have a genotype-specific activity and they may select rapidly drug-resistant variants if HCV replication is not completely suppressed. Nonetheless, they provide additional options for

addressing the needs of infected patients. **TAKE HOME MESSAGE:** NS5B polymerase inhibitors will form an integral part of more effective anti-HCV therapy, in combination with interferon or with other directly acting antiviral agents.

Sensory neuropathy in patients with cryoglobulin negative hepatitis-C infection.

Yoon MS, Obermann M, Dockweiler C, et al. *J Neurol.* 2010 Aug 4. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20683606>

There is growing evidence that hepatitis-C virus (HCV) infection might cause peripheral neuropathy. We aimed to investigate the prevalence, clinical and electrophysiological features of sensory neuropathy in patients with cryoglobulin negative HCV infection. We studied 46 consecutive cryoglobulin negative HCV positive patients (24 of them with and 22 without neuropathic symptoms, NS) and compared to 28 age and gender matched controls. In all patients and controls, clinical neuropathy symptom (NSS) and neuropathy deficit scores (NDS) were assessed and standard nerve conduction velocity (SNCV) and pain related-evoked potentials (PREP) were recorded. Both, SNCV and PREP were abnormal in 13 NS positive patients (13/46, 28%). Abnormal PREP but normal SNCV were found in 5 (5/46, 11%) NS positive and in 2 NS negative patients (2/46, 4%). PREP abnormalities correlated positive with both clinical neuropathy scores (NSS $r = 0.62$; $p < 0.001$; NDS $r = 0.57$; $p < 0.001$), but not with the duration of the disease, current viral load, or the virus subtype. PREP abnormalities were more frequent (16/33, 48.5%) in HCV patients treated with interferon than in therapy naïve patients (4/13, 30.8%); the difference was, however, not significant. In our present study (1) all virus subtypes are capable of inducing neuropathy, (2) no differences were found between interferon therapy and treatment naïve patients, (3) the prevalence of peripheral sensory neuropathy including small sensory fibers (20/46, 43.5%) is higher than previously reported and (4) we found that detection of HCV associated neuropathy depends on the evaluation method.

Effect of aging on risk for hepatocellular carcinoma in chronic hepatitis C virus infection.

Asahina Y, Tsuchiya K, Tamaki N, et al. *Hepatology.* 2010 Aug;52(2):518-27.

<http://www.ncbi.nlm.nih.gov/pubmed/20683951>

An increase in the aging population is an impending problem. A large cohort study was carried out to determine the influence of aging and other factors on hepatocarcinogenesis in patients treated with interferon. Biopsy-proven 2547 chronic hepatitis C patients registered at our referral center since 1992 were included. Of these, 2166 were treated with interferon-based therapy. Incidences of hepatocellular carcinoma (HCC) associated with interferon were analyzed by Kaplan-Meier and person-years methods for an average follow-up of 7.5 years. Factors associated with HCC risk were determined by Cox proportional hazard analysis. HCC developed in 177 interferon-treated patients. The risk for HCC depended on age at primary biopsy and increased more than 15-fold after 65 years of age. Even when stratified by stage of fibrosis, the cumulative and annual incidences of HCC were significantly higher in older patients than in younger patients ($P < 0.001$) at the same stage of fibrosis, except for cirrhosis. Progression of fibrosis over time was significantly accelerated in older patients. The impact of viral eradication on HCC prevention was less significant in older patients than in younger patients. Multivariate analysis confirmed that age, gender, liver fibrosis, liver steatosis, total cholesterol level, fasting blood sugar level, baseline and postinterferon alpha-fetoprotein level, and virological response to interferon were independent risk factors associated with HCC. Aging was the strongest risk factor for a nonvirological response to interferon-based antiviral therapy. **CONCLUSION:**

Elderly patients are at a higher risk for HCC. Hepatitis C viral eradication had a smaller effect on hepatocarcinogenesis in older patients. Patients should therefore be identified at an earlier age and treatment should be initiated.

Predictors of Early Treatment Discontinuation Among Patients with Genotype 1 Hepatitis C and Implications for Viral Eradication. Beste LA, Ioannou GN, Larson M, Chapko M, Dominitz JA. Clin Gastroenterol Hepatol. 2010 Aug 5. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20692371>

BACKGROUND & AIMS: A significant proportion of patients with hepatitis C virus (HCV) infection discontinue antiviral treatment prematurely. Risk factors for discontinuation before 48 weeks among patients with genotype 1 HCV vary over the course of therapy. We investigated the rates and risk factors for treatment discontinuation within 12 weeks, 12-24 weeks, and 24-48 weeks after therapy began. **METHODS:** We retrospectively evaluated data from all Veterans Affairs (VA) patients with genotype 1 HCV who initiated pegylated interferon and ribavirin therapy from 2002 to 2007 (n=11,019). We accounted for appropriate discontinuation because of lack of viral response. **RESULTS:** Overall, 53% of patients completed at least 38.4 weeks of therapy (80% of the projected 48 weeks), 16.5% discontinued early because of viral nonresponse, and 30.9% discontinued despite viral response or in the absence of virologic data. Cirrhosis, diabetes, pre-treatment substance use disorder, lower baseline concentration of hemoglobin, and lack of hematopoietic growth factor use independently predicted discontinuation within the first 12 weeks (P<.05 for all). Among patients with documented early virologic responses, higher baseline levels of creatinine, depression, and lack of growth factor use predicted discontinuation from 12 to 24 weeks. No factors independently predicted discontinuation from 24 to 48 weeks among patients that responded to treatment at 24 weeks. **CONCLUSION:** Early discontinuation of antiviral therapy is common. Use of growth factors was the strongest independent predictor of treatment retention before 24 weeks and should be evaluated prospectively. Early interventions are also warranted for other risk factors for early discontinuation, such as pre-existing substance use, depression, comorbid cirrhosis, or diabetes.

Impact of IL28B genotype on the early and sustained virologic response in treatment-naïve patients with chronic hepatitis C. Stättermayer AF, Stauber R, Hofer H, et al. Clin Gastroenterol Hepatol. 2010 Aug 19. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20728570>

BACKGROUND & AIMS: Single nucleotide polymorphisms (SNPs) in the gene that encodes interleukin (IL)28B predict response of patients with chronic Hepatitis C to antiviral therapy. We investigated the roles of polymorphisms rs12979860 and rs8099917 on the early virologic response of treatment-naïve patients. **METHODS:** SNPs rs12979860 and rs8099917 were identified by real-time PCR analysis of samples from 682 patients (genotype[GT]1=372, GT2/3=208, GT4=102) who were treated with 180 mug peg-interferon-alpha2a and 400 or 800 mg (GT2/3, depending on the protocol) or 1000-1200 mg (GT1/4) ribavirin/day. The duration of treatment was 24 (GT2/3) or 24-72 weeks (GT1/4). **RESULTS:** The decrease in virus 24 hours after the first dose of interferon in patients with GT1/4 was greater in carriers of the C/C than of the T allele (mean GT1: 1.28+/-0.49 log IU/ml vs. 0.77+/-0.49; GT4: 1.60+/-0.59 vs.0.77+/-0.55; both P<0.001); the patients with the C/C allele also had higher rates of a rapid virologic response (RVR) (GT1: 38.3% vs. 11.6%; GT4: 76.5% vs. 23.5%, both P<0.001) and sustained virologic responses (SVR) (GT1: 79.1% vs. 43.2%; GT4: 85.3% vs. 44.1%, both P<0.001). In patients

with GT2/3, the RVR was more frequent in carriers of rs12979860 C/C (75.3% vs. 52.6%, $P < 0.01$) but SVR rates were similar between those with C/C and T (80.5% vs. 74.4%, $P = 0.31$). Results for rs8099917 were comparable. The positive predictive value of rs12979860 C/C for SVR was higher than of rs8099917 T/T (80.5% vs. 71.6%). Overall, RVR was the best predictor of SVR. In patients that did not have GT1, IL28B polymorphisms did not affect the SVR, if RVR data were included in the multivariate analysis. **CONCLUSION:** An early virologic response to peginterferon and ribavirin is more likely among carriers of IL28 polymorphisms rs12979860 C/C and rs8099917 T/T, which might underlie their high rates of SVR. Determination of the IL28B genotype and whether patients have a RVR might be used in future studies of patients with Hepatitis C virus genotypes 1 or 4.

Secondary structure of the amino-terminal region of HCV NS3 and virological response to pegylated interferon plus ribavirin therapy for chronic hepatitis C. Sanjo M, Saito T, Ishii R, et al. *J Med Virol.* 2010 Aug;82(8):1364-70.

<http://www.ncbi.nlm.nih.gov/pubmed/20572079>

The aim of the study was to identify a predictive marker for the virological response in hepatitis C virus 1b (HCV-1b)-infected patients treated with pegylated interferon plus ribavirin therapy. A total of 139 patients with chronic hepatitis C who received therapy for 48 weeks were enrolled. The secondary structure of the 120 residues of the amino-terminal HCV-1b non-structural region 3 (NS3) deduced from the amino acid sequence was classified into two major groups: A and B. The association between HCV NS3 protein polymorphism and virological response was analyzed in patients infected with group A ($n = 28$) and B ($n = 40$) isolates who had good adherence to both pegylated interferon and ribavirin administration ($>95\%$ of the scheduled dosage) for 48 weeks. A sustained virological response (SVR) representing successful HCV eradication occurred in 33 (49%) in the 68 patients. Of the 28 patients infected with the group A isolate, 18 (64%) were SVR, whereas of the 40 patients infected with the group B isolate only 15 (38%) were SVR. The proportion of virological responses differed significantly between the two groups ($P < 0.05$). **These results suggest** that polymorphism in the secondary structure of the HCV-1b NS3 amino-terminal region influences the virological response to pegylated interferon plus ribavirin therapy, and that virus grouping based on this polymorphism can contribute to prediction of the outcome of this therapy.

Hepatocellular carcinoma in individuals with HBV infection or HBV-HCV co-infection in a low endemic country. Davídsdóttir L, Duberg AS, Törner A, et al. *Scand J Gastroenterol.* 2010 Aug;45(7-8):944-52.

<http://www.ncbi.nlm.nih.gov/pubmed/20384529>

OBJECTIVE: The aim of this nationwide cohort study was to assess the risk for hepatocellular carcinoma (HCC) in patients with chronic hepatitis B virus (HBV) infection or HBV and hepatitis C virus (HCV) co-infection in Sweden, a low endemic country. **MATERIAL AND METHODS:** A total of 12,080 patients with HBV and 3238 patients with HBV-HCV co-infection were notified to the Swedish institute for Infectious Disease Control between 1990 and 2004. After excluding 1850 patients with acute HBV and 584 patients infected in adult life, we analyzed the cohort of 9646 subjects with chronic HBV infection. In the co-infection cohort, 1697 patients were analyzed after excluding 1541 cases with acute HBV. The Swedish national cancer registry was used for follow-up. The HCC incidence rate in the cohorts was compared with the HCC incidence rate in the general population and the standardized incidence ratio (SIR)

was calculated for different strata according to estimated infection period. **RESULTS:** HCC was found in 45 patients in the HBV cohort. In the stratum of 40-49 years of infection we found a SIR of 47 and in stratum 50-59 years the SIR was 54. In the co-infected cohort 10 HCCs were found. The SIR in the stratum 20-29 years of infection was 34 and the SIR in the stratum 30 years and over was 91. **CONCLUSIONS:** This national cohort study of HBV infected and HBV-HCV co-infected subjects in a low endemic country confirms a highly increased risk of liver cancer compared to the general population.

Development and progression of gastroesophageal varices in patients with chronic hepatitis C.

C. Gentile I, Borgia G. *Expert Rev Anti Infect Ther.* 2010 Aug;8(8):867-70.

<http://www.ncbi.nlm.nih.gov/pubmed/20695740>

Hepatitis C virus infection is the leading cause of chronic liver disease in the western world. Chronic liver diseases may cause, through portal hypertension, the development of gastroesophageal varices, which can then bleed. We assess the findings of a study aimed at identifying the incidence of de novo varix development and their progression in patients with chronic hepatitis C and advanced fibrosis. This study was a substudy of the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) trial. The HALT-C trial was designed to determine whether pegylated interferon (PEG-IFN) at low dose can reduce the rate of disease progression in these patients. Approximately 26% of patients developed de novo varices and 35.2% of patients with varices at baseline had variceal progression or bleeding during the 4-year follow-up. The authors examine demographic, clinical, laboratory, virological, endoscopic and histological factors associated with the development and progression of gastroesophageal varices. PEG-IFN-alpha2a therapy did not reduce the risk of development or progression of gastroesophageal varices.

Evaluation of depression as a risk factor for treatment failure in chronic hepatitis C.

Leutscher PD, Lagging M, Buhl MR, et al. *Hepatology.* 2010 Aug;52(2):430-5.

<http://www.ncbi.nlm.nih.gov/pubmed/20683942>

The Major Depression Inventory (MDI) was used to estimate the value of routine medical interviews in diagnosing major depression among patients receiving peginterferon alfa-2a and ribavirin therapy for chronic hepatitis C virus (HCV) infection (n = 325). According to criteria from the MDI and Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), 19 patients (6%) had major depression at baseline. An additional 114 (37%) developed depression while on HCV combination therapy, with baseline MDI score and female sex independently predicting the emergence of major depression during treatment in a multivariate analysis. Only 36 (32%) of the 114 patients developing major depression according to MDI/DSM-IV criteria were correctly diagnosed during routine medical interviews. The emergence of major depression frequently led to premature discontinuation of peginterferon/ribavirin therapy, and an on-treatment MDI score increment exceeding 30 points (i.e., a validated marker of idiopathic DSM-IV major depression) was correlated with impaired outcome of HCV therapy (P = 0.02). This difference was even more pronounced among patients with an on-treatment increase in MDI score greater than 35 points (P = 0.003). **CONCLUSION:** We conclude that (1) depressive symptoms among patients undergoing HCV therapy are commonly overlooked by routine clinical interviews, (2) the emergence of depression compromises the outcome of HCV therapy, and (3) the MDI scale may be useful in identifying patients at risk for treatment-induced depression.

Effect of HCV infection on the mRNA expression of drug transporters and cytochrome P450 enzymes in chimeric mice with humanized liver. Kikuchi R, McCown M, Olson P, et al. *Drug Metab Dispos.* 2010 Aug 6. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20693416>

The expression of drug transporters and metabolizing enzymes are a primary determinant of drug disposition. Chimeric mice with humanized liver, including PXB mice, are an available model which is permissive to the in vivo infection of hepatitis C virus (HCV), thus being a promising tool for investigational studies in development of new antiviral molecules. To investigate the potential of HCV infection to alter the pharmacokinetics of small molecule antiviral therapeutics in PXB mice, we have comprehensively determined the mRNA expression profiles of human ATP-binding cassette (ABC) transporters, solute carrier (SLC) transporters, and cytochrome P450 enzymes (CYP) in the livers of these mice under non-infected and HCV-infected conditions. Infection of PXB mice with HCV resulted in an increase in the mRNA expression levels of a series of interferon-stimulated genes in the liver. For the majority of genes involved in drug disposition, minor differences in the mRNA expression of ABC and SLC transporters as well as CYPs between the non-infected and HCV-infected groups were observed. The exceptions were statistically significantly higher expression of MRP4 and OATP2B1 and lower expression of OCT1 and CYP2D6 in HCV-infected mice. Furthermore, the enzymatic activities of major human CYPs were in general comparable in the two experimental groups. These data suggest that the pharmacokinetic properties of small molecule antiviral therapies in HCV-infected PXB mice are likely to be similar to those in non-infected PXB mice. However, caution is needed in the translation of this relationship to HCV-infected patients as the PXB mouse model does not accurately reflect the pathology of chronic HCV patients.

c-Jun mediates hepatitis C virus hepatocarcinogenesis through signal transducer and activator of transcription 3 and nitric oxide-dependent impairment of oxidative DNA repair. Machida K, Tsukamoto H, Liu JC, et al. *Hepatology.* 2010 Aug;52(2):480-92.

<http://www.ncbi.nlm.nih.gov/pubmed/20683948>

Hepatocellular carcinoma (HCC) occurs in a significant number of patients with hepatitis C virus (HCV) infection. HCV causes double-strand DNA breaks and enhances the mutation frequency of proto-oncogenes and tumor suppressors. However, the underlying mechanisms for these oncogenic events are still elusive. Here, we studied the role of c-Jun, signal transducer and activator of transcription 3 (STAT3), and nitric oxide (NO) in spontaneous and diethylnitrosamine (DEN)-initiated and/or phenobarbital (Pb)-promoted HCC development using HCV core transgenic (Tg) mice. The viral core protein induces hepatocarcinogenesis induction as a tumor initiator under promotion by Pb treatment alone. Conditional knockout of c-jun and stat3 in hepatocytes achieves a nearly complete, additive effect on prevention of core-induced spontaneous HCC or core-enhanced HCC incidence caused by DEN/Pb. Core protein induces hepatocyte proliferation and the expression of inflammatory cytokines (interleukin-6, tumor necrosis factor-alpha, interleukin-1) and inducible NO synthase (iNOS); the former is dependent on c-Jun and STAT3, and the latter on c-Jun. Oxidative DNA damage repair activity is impaired by the HCV core protein due to reduced DNA glycosylase activity for the excision of 8-oxo-2'-deoxyguanosine. This impairment is abrogated by iNOS inhibition or c-Jun deficiency, but aggravated by the NO donor or iNOS-inducing cytokines. The core protein also suppresses

apoptosis mediated by Fas ligand because of c-Jun-dependent Fas down-regulation. Conclusion: **These results indicate** that the HCV core protein potentiates chemically induced HCC through c-Jun and STAT3 activation, which in turn, enhances cell proliferation, suppresses apoptosis, and impairs oxidative DNA damage repair, leading to hepatocellular transformation.

Ultrastructural and biophysical characterization of hepatitis c virus particles produced in cell culture. Gastaminza P, Dryden K, Boyd B, Wood M, Law M, Yeager M, Chisari FV. J Virol. 2010 Aug 4. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20686033>

We analyzed the biochemical and ultrastructural properties of hepatitis C virus (HCV) particles produced in cell culture. Negative-stain electron microscopy (EM) revealed that the particles were spherical (approximately 40 - 75 nm diameter), pleomorphic, and that some of them contain HCV E2 protein and apolipoprotein E (apoE) on their surface. Electron cryomicroscopy (cryoEM) revealed two major particle populations, approximately 60 and approximately 45 nm in diameter. The approximately 60 nm particles were characterized by a membrane bilayer (presumably an envelope) that is spatially separated from an internal structure (presumably a capsid), and they were enriched in fractions that displayed a high infectivity-to-HCV RNA ratio. The approximately 45 nm particles lacked a membrane bilayer, displayed a higher buoyant density and a lower infectivity-to-HCV RNA ratio. We also observed a minor population of very low density >100 nm diameter vesicular particles that resemble exosomes. This study provides low resolution ultrastructural information of particle populations displaying differential biophysical properties and specific infectivity. Correlative analysis of the abundance of the different particle populations with infectivity, HCV RNA and viral antigens suggest that infectious particles are likely to be present in the large approximately 60 nm HCV particle populations displaying a visible bilayer. Our study constitutes an initial approach towards understanding the structural characteristics of infectious HCV particles.

Expression, purification and immunogenic characterization of hepatitis C virus recombinant E1E2 protein expressed by Pichia pastoris yeast. Cai W, Su L, Liao Q, Ye L, Wu Y, Wu Z, She Y. Antiviral Res. 2010 Aug 5. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20691736>

Development of an effective vaccine may be the key in the control of hepatitis C virus (HCV) infection. Recent studies have shown that HCV envelope proteins can induce broadly neutralizing antibodies against conserved domain for HCV binding to the cellular receptors. So HCV envelope proteins are considered as the major HCV vaccine candidate. In this study, we used Pichia pastoris yeast to express truncated HCV E1E2 protein, which consists of E1 residues 187-346 and E2 residues 381-699. The yeast can produce high level of recombinant HCV E1E2 protein. The protein has complex glycosylation and can bind to CD81, the putative HCV receptor. Moreover, the purified protein can efficiently induce anti-E1E2 antibodies in rabbits, which are able to neutralize two kinds of HCV pseudotype particles derived from HCV genotype 1a and 1b, as well as HCV virions derived from HCV genotype 2a. These findings indicate that the recombinant E1E2 glycoprotein is effective in inducing broadly neutralizing antibodies, and is a potent HCV vaccine candidate.

Amino acid substitution in hepatitis C virus core region and genetic variation near the interleukin 28B gene predict viral response to telaprevir with peginterferon and ribavirin.

Akuta N, Suzuki F, Hirakawa M, et al. Hepatology. 2010 Aug;52(2):421-9.

<http://www.ncbi.nlm.nih.gov/pubmed/20648473>

Genetic variation near the IL28B gene and substitution of amino acid (aa) 70 and 91 in the core region of hepatitis C virus (HCV) genotype 1b can predict the response to pegylated interferon (PEG-IFN)/ribavirin combination therapy, but its impact on triple therapy of telaprevir/PEG-IFN/ribavirin is not clear. The aims of this study were to investigate the predictive factors of sustained virological response to a 12-week or 24-week regimen of triple therapy in 72 of 81 Japanese adults infected with HCV genotype 1. Overall, sustained virological response and end-of-treatment response were achieved by 61% and 89%, respectively. Especially, the sustained virological response was achieved by 45% and 67% in the 12- and 24-week regimens, respectively. Multivariate analysis identified rs8099917 near the IL28B gene (genotype TT) and substitution at aa 70 (Arg70) as significant determinants of sustained virological response. Prediction of response to therapy based on a combination of these factors had high sensitivity, specificity, and positive and negative predictive values. The efficacy of triple therapy was high in the patients with genotype TT, who accomplished sustained virological response (84%), irrespective of substitution of core aa 70. In the patients having genotype non-TT, those of Arg70 gained high sustained virological response (50%), and sustained virological response (12%) was the worst in patients who possessed both genotype non-TT and Gln70(His70). **CONCLUSION:** This study identified genetic variation near the IL28B gene and aa substitution of the core region as predictors of sustained virological response to a triple therapy of telaprevir/PEG-IFN/ribavirin in Japanese patients infected with HCV genotype 1b.

HLA class I allele associations with HCV genetic variants in patients with chronic HCV genotypes 1a or 1b infection. Lange CM, Roomp K, Dragan A, et al. J Hepatol. 2010 Aug 3.

[Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20800922>

BACKGROUND & AIMS: The adaptive immune response against hepatitis C virus (HCV) is significantly shaped by the host's composition of HLA-alleles with the consequence that the HLA phenotype is a critical determinant of viral evolution during adaptive immune pressure. In the present study, we aimed to identify associations of HLA class I alleles with HCV subtypes 1a and 1b genetic variants. **METHODS:** The association between HCV genetic variants and specific HLA-alleles was investigated in a cohort of 159 patients with chronic HCV genotypes 1a- and 1b-infection who were treated with pegylated interferon-alfa 2b and ribavirin in a prospective controlled trial for 48weeks by direct sequencing of the genes encoding the HCV proteins E2, NS3, and NS5B and by HLA class I-genotyping of patients. HCV genetic variants were associated with specific HLA-alleles and the binding strength of accordant amino acid sequences to the corresponding HLA-allele was assessed by using the SYFPEITHI-algorithm. **RESULTS:** Overall, associations between HLA class I alleles and HCV sequence variation were rare. Five unknown HLA class I-associated viral genetic variations were identified, which in part affected the binding of predicted HCV CD8+ T cell epitopes to the respective HLA-allele. In addition, different patterns of HLA class I-allele/HCV sequence associations between the two subtypes were observed. **CONCLUSIONS:** We identified several unknown HLA class I-restricted HCV variants which in part impair binding to predicted HCV CD8+ T cell epitopes with remarkable differences between HCV subtypes 1a and 1b quasispecies.

Human immunodeficiency virus (HIV)-1 infects human hepatic stellate cells and promotes collagen I and monocyte chemoattractant protein-1 expression: implications for the pathogenesis of HIV/hepatitis C virus-induced liver fibrosis. Tuyama AC, Hong F, Saiman Y, et al. *Hepatology*. 2010 Aug;52(2):612-22.

<http://www.ncbi.nlm.nih.gov/pubmed/20683959>

Patients coinfecting with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) develop more rapid fibrosis than those infected with HCV only. In HIV/HCV-coinfecting patients, fibrosis progression correlates with HIV RNA levels, suggesting a direct role of HIV in liver fibrogenesis. Chemokine (C-C motif) receptor 5 (CCR5) and cysteine-X-cysteine receptor 4 (CXCR4), the two major coreceptors required for HIV entry into cells, are expressed on activated hepatic stellate cells (HSCs), the principle fibrogenic cell type in the liver. We therefore examined whether HIV can infect HSCs, explored the potential mechanisms of viral entry, and assessed the impact of infection as reflected by the ability of HSCs to transfer virus to T lymphocytes and elicit a proinflammatory and profibrogenic response. **We report** that the laboratory-adapted viruses HIV-IIIB (CXCR4-tropic or X4) and HIV-BaL (CCR5-tropic or R5) and primary HIV isolates can infect both a human stellate cell line, LX-2, and primary human HSCs. HIV entry and gene expression in HSCs was confirmed using HIV-green fluorescent protein (GFP) expression viral constructs in the presence or absence of the reverse-transcriptase inhibitor azidothymidine. CD4 expression on a subset of primary HSCs was demonstrated using fluorescence-activated cell sorting and immunofluorescence staining. Blocking experiments in the presence of anti-CD4, anti-CXCR4, and anti-CCR5 revealed that HIV entry into HSCs is predominantly CD4/chemokine coreceptor-independent. HIV infection promoted HSC collagen I expression and secretion of the proinflammatory cytokine monocyte chemoattractant protein-1. Furthermore, infected LX-2 cells were capable of transferring GFP-expressing virus to T lymphocytes in a coculture system. **CONCLUSION:** Taken together, our results suggest a potential role of HIV in liver fibrosis/inflammation mediated through effects on HSCs. The role of early highly active antiretroviral therapy initiation in patients with HIV/HCV coinfection warrants further investigation.

Can serum hyaluronic acid replace simple non-invasive indexes to predict liver fibrosis in HIV/Hepatitis C coinfecting patients? Resino S, Bellon JM, Asensio C, et al. *BMC Infect Dis*. 2010 Aug 19;10(1):244. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20723207>

BACKGROUND: Hyaluronic acid (HA) serum levels correlate with the histological stages of liver fibrosis in hepatitis C virus (HCV) mono-infected patients, and HA alone has shown very good diagnostic accuracy as a non-invasive assessment of fibrosis and cirrhosis. The aim of this study was to evaluate serum HA levels as a simple non-invasive diagnostic test to predict hepatic fibrosis in HIV/HCV-coinfecting patients and to compare its diagnostic performance with other previously published simple non-invasive indexes consisting of routine parameters (HGM-1, HGM-2, Forns, APRI, and FIB-4). **METHODS:** We carried out a cross-sectional study on 201 patients who all underwent liver biopsies and had not previously received interferon therapy. Liver fibrosis was determined via METAVIR score. The diagnostic accuracy of HA was assessed by area under the receiver operating characteristic curves (AUROCs). **RESULTS:** The distribution of liver fibrosis in our cohort was 58.2% with significant fibrosis (F[greater than or

equal to]2), 31.8% with advanced fibrosis (F[greater than or equal to]3), and 11.4% with cirrhosis (F4). Values for the AUROC of HA levels corresponding to significant fibrosis (F[greater than or equal to]2), advanced fibrosis (F[greater than or equal to]3) and cirrhosis (F4) were 0.676, 0.772, and 0.863, respectively. The AUROC values for HA were similar to those for HGM-1, HGM-2, FIB-4, APRI, and Forns indexes. The best diagnostic accuracy of HA was found for the diagnosis of cirrhosis (F4): the value of HA at the low cut-off (1182 ng/mL) excluded cirrhosis (F4) with a negative predictive value of 99% and at the high cut-off (2400 ng/mL) confirmed cirrhosis (F4) with a positive predictive value of 55%. By utilizing these low and high cut-off points for cirrhosis, biopsies could have theoretically been avoided in 52.2% (111/201) of the patients. **CONCLUSIONS:** The diagnostic accuracy of serum HA levels increases gradually with the hepatic fibrosis stage. However, HA is better than other simple non-invasive indexes using parameters easily available in routine clinical practice only for the diagnosing of cirrhosis.

Similar Progression of Fibrosis between HIV/HCV- and HCV-Infected Patients: Analysis of Paired Liver Biopsy Samples. Sterling RK, Wegelin JA, Smith PG, et al. Clin Gastroenterol Hepatol. 2010 Aug 19. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20728569>

BACKGROUND AND AIMS: Fibrosis progression might be accelerated in patients that are co-infected with HIV and hepatitis C virus (HIV/HCV). However, no studies have directly compared fibrosis progression by paired liver biopsy between patients infected with HIV and HCV vs. those infected with only HCV. **METHODS:** Liver biopsy samples were collected from patients with HIV/HCV (n=306) and those with HCV; biopsies from 59 without a sustained virologic response (SVR) or cirrhosis were matched with those from patients with only HCV (controls) for initial fibrosis stage, demographics, and HCV treatment. For HIV/HCV patients, categorical variables at baseline and the area under the curve of continuous variables per unit time were analyzed for associations with fibrosis progression. **RESULTS:** Liver biopsies from HIV/HCV patients had more piecemeal necrosis than controls (P=.001) and increased lobular inflammation (P=.002); HIV/HCV patients also had shorter intervals between liver biopsies (4.7 vs. 5.9 yrs, P<.0001). Between the 1st and 2nd biopsies, fibrosis remained unchanged or progressed 1 or 2 units in 55%, 18%, and 18% of HIV/HCV patients, respectively, compared with 45%, 30%, and 9% of controls. The fibrosis progression rate was similar between HIV/HCV and control patients (0.12+/-0.40 vs. 0.091+/-0.29 units/yr; P=.72). In paired biopsies from 66 patients, including those with SVR, there were no associations between fibrosis progression and demographics; numbers of CD4+ T cells; levels of aspartate aminotransferase or alanine aminotransferase; use of highly-active anti-retroviral therapy; response to HCV therapy (no treatment, SVR, or non-response); baseline levels of FIB-4; or histological features including inflammation, fibrosis, or steatosis. **CONCLUSIONS:** Based on analysis of liver biopsy samples, fibrosis progression was similar between HIV/HCV- and HCV-infected patients; no clinical or laboratory parameters predicted disease progression.

Very early prediction of response to HCV treatment with PEG-IFN-alfa-2a and ribavirin in HIV/HCV-coinfected patients. Araújo ES, Dahari H, Neumann AU, et al. *J Viral Hepat.* 2010 Aug 3. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20738775>

The objective of this study was to find very early viral kinetic markers to predict nonresponse to hepatitis C virus (HCV) therapy in a group of human immunodeficiency virus (HIV)/HCV-coinfected patients. Twenty-six patients (15 HCV genotype-1 and 11 genotype-3) were treated with a 48-week regimen of peginterferon-alfa-2a (PEG-IFN) (180 mug/week) and weight-based ribavirin (11 mg/kg/day). Samples were collected at baseline; 4, 8, 12, 18, 24, 30, 36 and 42 h; days 2, 3, 4, 7, 8, 15, 22, 29, 43 and 57 then weekly and monthly. Five patients discontinued treatment. Seven patients (27%) achieved a sustained virological response (SVR). Nadir HCV RNA levels were observed 1.6 +/- 0.3 days after initiation of therapy, followed by a 0.3- to 12.9-fold viral rebound until the administration of the second dose of PEG-IFN, which were not associated with SVR or HCV genotype. A viral decline <1.19 log for genotype-1 and <0.97 log for genotype-3, 2 days after starting therapy, had a negative predictive value (NPV) of 100% for SVR. The day 2 virological response had a similar positive predictive value for SVR as a rapid virological response at week 4. In addition, a second-phase viral decline slope (i.e., measured from day 2 to 29) <0.3 log/week had a NPV = 100% for SVR. **We conclude that** first-phase viral decline at day 2 and second-phase viral decline slope (<0.3 log/week) are excellent predictors of nonresponse. Further studies are needed to validate these viral kinetic parameters as early on-treatment prognosticators of nonresponse in patients with HCV and HIV.

Relating the liver damage with hepatitis C virus polymorphism in core region and human variables in HIV-1-coinfected patients. Matas M, Picornell A, Cifuentes C, et al. *Infect Genet Evol.* 2010 Aug 20. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20732459>

Hepatitis C virus (HCV) infection is the most important cause of chronic hepatitis, cirrhosis and end-stage liver disease leading to liver transplantation world-wide. Chronic infection by HCV causes liver fibrosis, which is accelerated by unknown mechanisms in patients with human immunodeficiency virus-1 (HIV-1) coinfection. Although the genetic variability of both HCV and HIV has been extensively studied in the context of mono-infections, more limited data is available regarding HCV-HIV coinfection. HCV disease progression among HIV coinfecting patients may be influenced not only by demographic, epidemiological and clinical background variables, but also by genetic differences in infecting viruses. To explore this issue, we carried out a study in coinfecting patients trying to associate the degree of liver damage to several demographic, clinical, and epidemiological characteristics of the patients, and also to the genetic variability of HCV between patients. For this purpose, we have applied different statistical techniques including the statistical generalized linear model (GLM) framework. The stage of fibrosis was indirectly measured by non-invasive means using the indexes Forns, APRI and FIB-4. HCV genetic variability between patients was estimated by sequencing the core region and by reconstructions of consensus maximum-parsimony phylogenetic trees with 50% and 75% bootstrap majority rules. The results showed a direct correlation of the fibrosis biomarkers with the AST/ALT ratio, MofitIDU and with 3a HCV genotype clades, among others.

Polymorphism in tumor necrosis factor-related apoptosis-inducing ligand receptor 1 is associated with poor viral response to interferon-based hepatitis C virus therapy in HIV/hepatitis C virus-coinfected individuals. Rizza SA, Cummins NW, Rider DN, et al.

AIDS. 2010 Aug 26. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20802294>

OBJECTIVE(S): HIV/hepatitis C virus (HCV) coinfection causes accelerated liver disease compared to HCV monoinfection, and only 30-60% of HIV/HCV-coinfected individuals respond to HCV therapy with pegylated interferon and ribavirin. There are currently no biomarkers that predict treatment response in these coinfecting patients. **DESIGN:** We investigated whether there is an association between HCV treatment response and SNPs of apoptosis-related genes during HIV/HCV coinfection. **METHOD:** Genomic DNA from 53 HIV/HCV-coinfected individuals was analyzed for 82 SNPs of 10 apoptosis-related genes. **RESULTS:** We found that the presence of the rs4242392 SNP in tumor necrosis factor receptor superfamily, member 10a (TNFRSF10A), which encodes for tumor necrosis factor-related apoptosis-inducing ligand receptor 1, predicts poor outcome to HCV therapy, in HIV/HCV-co-infected patients [odds ratio 5.91 (95% confidence interval 1.63-21.38, P = 0.007)]. **CONCLUSION:** The rs4242392 SNP of the tumor necrosis factor-related apoptosis-inducing ligand receptor 1 gene predicted poor interferon-based HCV treatment response in HIV/HCV-coinfected patients.

The cytotoxic lymphocyte antigen 4 polymorphisms affect response to hepatitis C virus-specific therapy in HIV(+) patients with acute and chronic hepatitis C virus co-infection.

Nischalke HD, Vogel M, Mauss S, et al. AIDS. 2010 Aug 24;24(13):2001-7.

<http://www.ncbi.nlm.nih.gov/pubmed/20588168>

OBJECTIVE: Cytotoxic lymphocyte antigen 4 (CTLA4), a co-receptor expressed on T lymphocytes, is involved in the regulation of T-cell functions. Here, we analyzed the potential impact of the CTLA4 polymorphisms on response to hepatitis C virus (HCV)-specific treatment in HIV(+) patients co-infected with HCV. **PATIENTS AND METHODS:** A total of 184 HIV/HCV co-infected Caucasian patients were enrolled into this study, including 109 patients with chronic and 75 patients with acute hepatitis C. CTLA4 genotypes were determined by LightCycler PCR. **RESULTS:** We found the CTLA4 -318 C/C genotype to be associated with sustained virological response in HCV/HIV co-infection (P = 0.035). Moreover, response rates were significantly higher in patients with a +49G/G genotype [23/29 (79.3%)] than in carriers of other +49 genotypes [59/155 (38.1%); OR 6.2; P = 0.00005]. Of note, the CTLA4 +49G/G genotype was confirmed as an independent predictor for treatment response in both patients with acute and chronic hepatitis C. **CONCLUSION:** CTLA4 polymorphisms are associated with treatment-induced resolution of HCV infection in HIV co-infected patients. These findings underline the impact of genetic host factors for successful treatment.

Hepatitis C virus infection is associated with endothelial dysfunction in HIV/hepatitis C virus coinfecting patients. de Castro IF, Micheloud D, Berenguer J, et al. AIDS. 2010 Aug 24;24(13):2059-67.

AIDS. 2010 Aug 24;24(13):2059-67.

<http://www.ncbi.nlm.nih.gov/pubmed/20616694>

OBJECTIVE: To quantify serum levels of intercellular adhesion molecule-1 (sICAM-1) and vascular cell adhesion molecule-1 (sVCAM-1) in HIV/HCV coinfecting patients to examine their association with several clinical and epidemiological characteristics and the therapeutic responsiveness to interferon (IFN)-alpha and ribavirin therapy (IFN-alpha + RBV).

DESIGN: Retrospective study. **METHODS:** We carried out a cross-sectional study with 183 IFN-alpha-naive patients on HAART, and 24 healthy controls. We also analyzed 30 out of 183 patients on IFN-alpha + RBV for the duration of 48 weeks. **RESULTS:** HIV/HCV coinfecting patients had higher levels of sICAM-1 and sVCAM-1 than the healthy control group ($P < 0.05$). Patients with HCV-genotype 1, advanced fibrosis ($F \geq 3$) or moderate to severe activity grade ($A \geq 2$) had the highest values of sICAM-1 and sVCAM-1. When we carried out a multivariate analysis, we found a significant positive relationship between both HCV-genotype 1 and advanced fibrosis ($F \geq 3$) with sICAM-1 ($R = 0.549$; $P < 0.001$); and a significant positive relationship between HCV-genotype 1 and advanced fibrosis ($F \geq 3$) with sVCAM-1 ($R = 0.624$; $P < 0.001$). We also found a positive relationship of sICAM-1 or sVCAM-1 levels with transaminases and alkaline phosphatase circulation levels ($P < 0.05$). Nonresponder patients had higher sICAM-1 and sVCAM-1 serum levels, and patients with sustained virologic response had significantly lower levels of sICAM-1 ($P = 0.001$) and sVCAM-1 ($P = 0.019$). **CONCLUSION:** HIV and HCV coinfection induces alterations in sICAM-1 and sVCAM-1 serum levels, which were higher in patients with HCV-genotype 1 and advanced stage of HCV infection. However, response to IFN-alpha + RBV may reduce these cardiovascular risk markers.

Clinical and biologic importance of F-actin autoantibodies in HCV monoinfected and HCV-HIV coinfecting patients. Hudacko RM, Alvarez GA, Talal AH, et al. *Am J Clin Pathol.* 2010 Aug;134(2):228-34.

<http://www.ncbi.nlm.nih.gov/pubmed/20660325>

The purpose of this study was to evaluate the relationship between serum filamentous (F)-actin antibody titers and severity of hepatitis present in hepatitis C virus (HCV)-infected patients. Liver biopsy samples from 18 HCV monoinfected and 20 HCV-HIV coinfecting patients were graded with respect to the degree of hepatitis activity and intensity of plasma cell infiltration using MUM-1 and CD138 immunostains. Of the 38 HCV-infected patients, 6 (16%) had F-actin antibody titers in excess of 30 enzyme-linked immunosorbent assay units. We found a positive trend between serum F-actin antibody levels and the mean number of plasma cells present in the portal tracts of patients with HCV infection ($r = 0.31$; $P = .06$) and a significant association between these factors in HCV-HIV coinfecting patients ($r = 0.64$; $P = .002$). **Our data suggest that** elevated serum F-actin antibody titers are commonly encountered in HCV-infected patients and may reflect more active inflammation in liver biopsy samples, similar to autoimmune hepatitis.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

Long-Term Management of Hepatitis C-Seropositive Subjects with AntiOxidant Biofactor (AOB(R)), a Fermented Food Supplement. Myo-Khin, Myat-Tin-Htwe-Kyaw, Yi-Yi-Kyaw, et al. *Acta Med Okayama.* 2010 Aug;64(4):243-8.

<http://www.ncbi.nlm.nih.gov/pubmed/20802541>

The efficacy of AntiOxidant Biofactor (AOB(R)) for the management of apparently healthy subjects with chronic hepatitis C infection was investigated. A total of 60 subjects (35 males, 25 females) participated in the trial. AOB was given orally in 2 packs (3g per pack) 3 times per day. 17 subjects had taken AOB for 3 years, 31 subjects up to 2 years, and 41 subjects up to one year. The initial mean (SD) serum alanine aminotransferase (ALT) level was 46.3 ± 35.4 IU/L, and significant ($p < 0.05$, paired t-test) reductions in the mean serum ALT levels were observed at 6

months (38.6+/-21.5IU/L), 18 months (31.9+/-18.1IU/L), 2 years (31.2+/-14.6IU/L), and 3 years (28.0+/-15.9IU/L). Those presenting with high serum ALT levels (30 subjects) demonstrated significant levels (p0.05, paired t-test) of reduction in the mean serum ALT levels at 6, 12, 18, 24, and 36 months of treatment. No side effects were observed and the AOB treatment was well tolerated by all subjects.

Procyanidin B1 purified from Cinnamomi cortex suppresses hepatitis C virus replication.

Li S, Kodama EN, Inoue Y, et al. *Antivir Chem Chemother*. 2010 Aug 11;20(6):239-48.

<http://www.ncbi.nlm.nih.gov/pubmed/20710064>

BACKGROUND: A combination of pegylated interferon and ribavirin is the current standard therapy for hepatitis C virus (HCV) infection, but this combination provides relatively low efficacy, especially in some patients with HCV genotype 1 infection; therefore, the development of novel therapeutic agents is required for further improvement in the treatment of chronic HCV infection. **METHODS:** HCV pseudotype and subgenomic replicon assays were used in this study. The interaction of compounds with HCV receptors was examined using flow cytometry. Intracellular RNA levels were determined by semi-quantitative reverse transcriptase PCR.

RESULTS: Procyanidin B1 (PB1), a dimer of (-)-epicatechin and (+)-catechin, purified from Cinnamomi cortex, inhibits infection by vesicular stomatitis virus and HCV pseudotype virus in Huh-7 cells, with 50% effective concentrations of 29 and 15 microM, respectively. No inhibitory effects were observed in each component of PB1. We found that PB1 does not interfere with viral entry or receptor expression, but inhibits HCV RNA synthesis in a dose-dependent manner.

CONCLUSIONS: These results indicate that PB1 suppresses HCV RNA synthesis, possibly as a HCV RNA polymerase inhibitor. Our results might contribute towards the development of more effective inhibitors for HCV infection from natural plants.

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

Real-time tissue elastography as a tool for the noninvasive assessment of liver stiffness in patients with chronic hepatitis C. Morikawa H, Fukuda K, Kobayashi S, et al. *J Gastroenterol*. 2010 Aug 10. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20697747>

BACKGROUND: Although histopathological examination by "invasive" liver biopsy remains the gold standard for evaluating disease progression in chronic liver disease, noninvasive tools have appeared and have led to great progress in diagnosing the stage of hepatic fibrosis. The aim of this study was to assess the value of real-time tissue elastography, using an instrument made in Japan, for the visible measurement of liver elasticity; in particular, comparing the results with those of transient elastography (Fibroscan). **METHODS:** Real-time tissue elastography (RTE), transient elastography (Fibroscan), liver biopsy, and routine laboratory analyses were performed in 101 patients with chronic hepatitis C. The values for tissue elasticity obtained using novel software (Elasto_ver 1.5.1) connected to RTE were transferred to four image features, Mean, Standard Deviation (SD), Area, and Complexity. Their association with the stage of fibrosis at biopsy and with liver stiffness (kPa) obtained by Fibroscan was analyzed. **RESULTS:** Colored images obtained by RTE were classified into diffuse soft, intermediate, and patchy hard patterns and the calculated elasticity differed significantly between patients according to and correlated with the stages of fibrosis (p < 0.0001). Mean, SD, Area, and Complexity showed significant differences between the stages of fibrosis (Tukey-Kramer test, p < 0.05). In discriminating

patients with cirrhosis, the areas under the receiver operating characteristic curves (AUC) were 0.91 for Mean, 0.84 for SD, 0.91 for Area, 0.93 for Complexity, and 0.95 for Fibroscan.

CONCLUSIONS: RTE is a noninvasive instrument for the colored visualization of liver elasticity in patients with chronic liver disease.

The impact of hepatitis C virus infection on work absence, productivity, and healthcare benefit costs. Su J, Brook RA, Kleinman NL, Corey-Lisle P. *Hepatology*. 2010 Aug;52(2):436-42.

<http://www.ncbi.nlm.nih.gov/pubmed/20683943>

Chronic hepatitis C virus (HCV) infection is generally considered an asymptomatic disease. However, studies have shown that HCV has a substantial negative impact on patients' quality of life and functioning. This study was designed to compare absenteeism, productivity, and health cost between employees with and without HCV infection in the United States. Employee records from multiple large employers in the United States were obtained from the Human Capital Management Services Research Reference Database and were assessed for demographics, salary, healthcare use, work loss, and workers' compensation. HCV-infected subjects were identified by International Classification of Diseases 9th revision Clinical Modification codes. Controls were randomly selected from employees not diagnosed with HCV. T-tests and chi-square tests were used to determine if there were differences in demographic characteristics. Regression modeling compared days absent (among benefit-eligible employees) and productivity (among employees with data on task-oriented activities), while controlling for the impact of confounding factors. A total of 339,456 subjects were evaluated. Employees with HCV (n = 1664) had significantly more lost work days per employee than the control cohort (n = 337,792), including sick leave, short-term disability, and long-term disability. HCV-infected workers had 4.15 more days of absence per employee than the control cohort. Productivity was measured by units of work processed per hour; employees with HCV processed 7.5% fewer units per hour than employees without HCV (P > 0.05). All healthcare benefit costs among HCV employees were significantly higher than the same costs among employees without HCV. Overall, the total incremental difference was \$8352 per year. **CONCLUSION:** This real world study provides evidence that there is a substantial indirect burden of illness and describes a relationship between HCV infection, productivity, increased absenteeism, and higher healthcare benefit costs.

Inflammatory bowel diseases and hepatitis C virus infection. Li YD, Lin JJ, Zheng SS. *Hepatobiliary Pancreat Dis Int*. 2010 Aug;9(4):398-401.

<http://www.ncbi.nlm.nih.gov/pubmed/20688604>

BACKGROUND: Data on the prevalence of hepatitis C in patients with inflammatory bowel diseases (IBD) are limited and conflicting. This study was to assess the prevalence of hepatitis C virus (HCV) infection in IBD patients and to define the clinical and immunologic profile of IBD associated with HCV infection. **METHODS:** Ten patients (seven females and three males) with IBD and HCV infection were consecutively recruited in our department between June 2005 and May 2010. We analyzed the clinical and serologic description of all patients. **RESULTS:** The mean age of the 10 patients was 41 years and the median disease duration was 7 years. With present and/or past HCV infection, the patients had clinical manifestations and were positive for endoscopic study or histological test. Compared with the HCV-negative IBD group, the HCV-positive IBD group have a higher positive rate of autoantibodies (antinuclear antibodies, antieutrophil cytoplasmic antibody, and anti-SSa/SSb). In the HCV-positive group, 8 patients

were positive for p-antitrophil cytoplasmic antibody, 4 positive for antinuclear antibodies, and 3 positive for anti-SSa/SSb. Four patients had an elevated level of transaminase (alanine transaminase, and aspartate transaminase). **CONCLUSIONS:** HCV positive in IBD may induce autoanti-bodies (antinuclear antibodies, antitrophil cytoplasmic antibody, anti-SSa/SSb) and damage of liver function. In managing IBD patients, physicians should be aware of screening of HCV and prescribe antiviral treatment.

Prevalence of hepatitis C in two inpatient psychiatry populations. Gunewardene R, Lampe L, Ilchef R. *Australas Psychiatry*. 2010 Aug;18(4):330-4.

<http://www.ncbi.nlm.nih.gov/pubmed/20645899>

OBJECTIVE: Psychiatric populations may be particularly at risk of hepatitis C (HCV), less likely to receive appropriate interventions and at greater risk of liver damage due to comorbid substance abuse. This study sought to determine the prevalence of HCV in two inpatient psychiatric populations of seriously mentally ill patients and the relationship to risk factor screening. **METHOD:** Two inpatient units were chosen in similar socio-economic areas. Persons admitted to these wards over the course of the study were invited to participate and provided with pre-test counselling. Where informed consent was obtained, individuals were included in the study. It was planned to screen all consenting patients. However, funding was reduced for one site meaning that only patients with identified risk factors could be screened there. **RESULTS:** Around 18% of psychiatric inpatients admitted to risk factors for HCV. The prevalence of HCV with screening of all consenting patients in unit A was 3.2%. With selective screening in unit B, 41.7% of those with identified risk factors tested positive. These results compare to the Australian community rate of approximately 1.1%. **CONCLUSION:** Results are consistent with elevated rates of HCV in mentally ill populations elsewhere in the world, and provide support for selective screening.

HCC develops even in the early stage of chronic liver disease in elderly patients with HCV infection. Takata A, Kuromatsu R, Ando E, et al. *Int J Mol Med*. 2010 Aug;26(2):249-56.

<http://www.ncbi.nlm.nih.gov/pubmed/20596605>

In recent years, the number of elderly patients with hepatocellular carcinoma (HCC) has been increasing. The aim of this study was to compare the liver function and the background factors of HCC patients with hepatitis C virus (HCV) infection by generation and to examine the characteristics of this disease in the elderly. A total of 1096 patients (776 men and 320 women) diagnosed with HCV-related HCC at our institution from 1995 to 2006 were divided into 4 groups as follows: D group, 75 years of age or older; C group, 65-74 years of age; B group, 55-64 years of age; A group, 54 years of age or younger, and the liver function and other clinical characteristics were compared among these 4 groups. The average age at initial diagnosis of HCV-related HCC was 66.9 years of age. The A, B, C and D groups were comprised of 87, 363, 514 and 132 patients, respectively. The rate of Child-Pugh class A patients in the D group was significantly higher than that of the other groups ($P < 0.05$). The average levels of ALT, TB and PT-INR in the D group were significantly lower than the levels in the other groups ($P < 0.05$). The average Alb level in the D group was significantly higher than that in the other groups ($P < 0.05$). **In conclusion**, we found that HCV-related HCC in the elderly occurred against a background of chronic liver disease with mild inflammation and fibrosis.

Development and evaluation of an automated hepatitis C virus NS5B sequence-based subtyping assay. Koletzki D, Dumont S, Vermeiren H, Fevery B, De Smet P, Stuyver LJ. Clin Chem Lab Med. 2010 Aug;48(8):1095-102.

<http://www.ncbi.nlm.nih.gov/pubmed/20578969>

BACKGROUND: Hepatitis C virus (HCV) genotyping and accurate subtype determination is becoming increasingly important to better understand viral evolution, the development of resistance to STAT-C, and possibly even for the treatment and management of chronic HCV-infected patients. **METHODS:** A subtyping assay based on a 329-bp sequence of the NS5B region, together with an automated subtype interpretation tool was developed. Clinical samples of the six major genotypes were used to assess assay performance characteristics. **RESULTS:** The NS5B BLAST-based subtyping assay showed clinical sensitivity for amplification of 89% (n=603 random samples). Assessment of analytical sensitivity of amplification for genotypes 1, 2, 3 and 4 revealed a suitable performance for high viral load samples and decreased only with low viral loads. The results were 100% and 99% accurate at the genotype and subtype level, respectively. A concordance of 97% on genotype level and 62% on subtype level was observed by comparison with subtype results from 5' non-coding-based assays with a panel of 276 isolates. **CONCLUSIONS:** The HCV NS5B subtyping assay has been validated for research use. Based on its performance, it is the method of choice in cases where subtype rather than genotype information is needed.

Survival of Hepatitis C Virus in Syringes: Implication for Transmission among Injection Drug Users. Paintsil E, He H, Peters C, Lindenbach BD, Heimer R. J Infect Dis. 2010 Aug 20. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20726768>

BACKGROUND: We hypothesized that the high prevalence of hepatitis C virus (HCV) among injection drug users might be due to prolonged virus survival in contaminated syringes. **METHODS:** We developed a microculture assay to examine the viability of HCV. Syringes were loaded with blood spiked with HCV reporter virus (Jc1/GLuc2A) to simulate 2 scenarios of residual volumes: low void volume (2 µL) for 1-mL insulin syringes and high void volume (32 µL) for 1-mL tuberculin syringes. Syringes were stored at 4 degrees C, 22 degrees C, and 37 degrees C for up to 63 days before testing for HCV infectivity by using luciferase activity. **RESULTS:** The virus decay rate was biphasic ([Formula: see text] h and [Formula: see text] h). Insulin syringes failed to yield viable HCV beyond day 1 at all storage temperatures except 4 degrees , in which 5% of syringes yielded viable virus on day 7. Tuberculin syringes yielded viable virus from 96%, 71%, and 52% of syringes after storage at 4 degrees , 22 degrees , and 37 degrees for 7 days, respectively, and yielded viable virus up to day 63. **CONCLUSIONS:** The high prevalence of HCV among injection drug users may be partly due to the resilience of the virus and the syringe type. Our findings may be used to guide prevention strategies.

Tobacco and other factors have a negative impact on quality of life in hepatitis C patients. Yamini D, Basseri B, Chee GM, et al. J Viral Hepat. 2010 Aug 15. [Epub ahead of print] Arakelyan A, Enayati P, Tran TT, Poordad F.

<http://www.ncbi.nlm.nih.gov/pubmed/20723039>

Hepatitis C virus (HCV) is known to adversely affect general, social, emotional and mental health domains. This study was designed to identify variables that may be associated with these measurable outcomes. We conducted a cross-sectional retrospective review of demographic and

clinical data from 800 patients with HCV evaluated between January 1998 and November 2007. Data were collected using a standardized questionnaire filled out by the patients at the first encounter. Variables evaluated included fibrosis stages (i.e. FS0/1/2 vs FS3/4), demographics, comorbid health conditions, tobacco and alcohol use, high-risk social behaviours and laboratory data. Variables assessed were depression, fatigue, problems sleeping and loss of interest in sex. Statistical analysis was performed using univariate and multivariate logistic regression. Depression (29.3%) in our HCV study population was associated with female gender, tobacco use, hyperlipidemia, history of heavy alcohol use and intravenous drug use. Fatigue (44.6%) was associated with end-stage renal disease, past and current tobacco use and current alcohol use. Difficulty sleeping (13.8%) was associated with past and current tobacco use, current alcohol use and diabetes. Loss of interest in sex (7.7%) was associated with current tobacco use, multiple risk factors for HCV and age at time of evaluation. Fibrosis stage (FS) also had a significant positive association with alcohol use (OR 2.61; P = 0.003) and tobacco use (OR 2.00; P = 0.002). Smoking and alcohol use have a significant negative impact on the presence of depression, fatigue, difficulty sleeping and loss of interest in sex in HCV patients. Practitioners should be aware of these associations, particularly tobacco use, which significantly and negatively impacted every variable evaluated.