



Caring Ambassadors Hepatitis C Program Newsletter

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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

Telaprevir for previously treated chronic HCV infection. McHutchison JG, Manns MP, Muir AJ, et al. N Engl J Med. 2010 Apr 8;362(14):1292-303.

<http://www.ncbi.nlm.nih.gov/pubmed/20375406>

BACKGROUND: Patients with genotype 1 hepatitis C virus (HCV) who do not have a sustained response to therapy with peginterferon alfa and ribavirin have a low likelihood of success with retreatment. **METHODS:** We randomly assigned patients with HCV genotype 1 who had not had a sustained virologic response after peginterferon alfa-ribavirin therapy to one of four treatment groups: 115 patients to the T12PR24 group, receiving telaprevir (1125-mg loading dose, then 750 mg every 8 hours) for 12 weeks and peginterferon alfa-2a (180 microg per week) and ribavirin (1000 or 1200 mg per day, according to body weight) for 24 weeks; 113 patients to the T24PR48 group, receiving telaprevir for 24 weeks and peginterferon alfa-2a and ribavirin for 48 weeks (at the same doses as in the T12PR24 group); 111 patients to the T24P24 group, receiving telaprevir and peginterferon alfa-2a for 24 weeks (at the same doses as in the T12PR24 group); and 114 patients to the PR48 (or control) group, receiving peginterferon alfa-2a and ribavirin for 48 weeks (at the same doses as in the T12PR24 group). The primary end point was sustained virologic response (undetectable HCV RNA levels 24 weeks after the last dose of study drugs). **RESULTS:** The rates of sustained virologic response in the three telaprevir groups--51% in the T12PR24 group, 53% in the T24PR48 group, and 24% in the T24P24 group--were significantly higher than the rate in the control group (14%; $P<0.001$, $P<0.001$, and $P=0.02$, respectively). Response rates were higher among patients who had previously had relapses than among nonresponders. One of the most common adverse events in the telaprevir groups was rash (overall, occurring in 51% of patients, with severe rash in 5%). Discontinuation of study drugs because of adverse events was more frequent in the telaprevir groups than in the control group (15% vs. 4%). **CONCLUSIONS:** In HCV-infected patients in whom initial peginterferon alfa and ribavirin treatment failed, retreatment with telaprevir in combination with peginterferon alfa-2a and ribavirin was more effective than retreatment with peginterferon alfa-2a and ribavirin alone.

Peginterferon alpha-2a Plus Ribavirin in Latino and Non-Latino Whites With HCV Genotype 1: Histologic Outcomes and Tolerability From the LATINO Study. Balart LA, Lisker-Melman M, Hamzeh FM, et al. *Am J Gastroenterol.* 2010 Apr 13. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/20389293>

OBJECTIVES: We sought to compare the histologic response, safety, and tolerability in Latino and non-Latino patients with hepatitis C virus (HCV) genotype 1 treated with peginterferon alpha-2a plus ribavirin (LATINO study). **METHODS:** LATINO was a prospective, open-label, multicenter study that enrolled 269 Latinos and 300 non-Latinos receiving peginterferon alpha-2a 180 mug/week and ribavirin 1,000/1,200 mg/day for 48 weeks. Liver biopsies were obtained within 18 months of baseline and at week 72. Improved or worsened liver fibrosis and necroinflammatory activity were assessed by the Ishak-modified histologic activity index scoring system. Efficacy and safety parameters were monitored during treatment and the 24-week follow-up period. **RESULTS:** The primary study results published elsewhere showed a higher sustained virologic response (SVR) rate among non-Latinos than Latinos (49% vs. 34%; $P < 0.001$). Paired biopsy data were available for 157 Latinos and 201 non-Latinos. At baseline, more Latinos vs. non-Latinos had alanine aminotransferase (ALT) > 3 x the upper limit of normal (20% vs. 18%) and cirrhosis (13% vs. 10%). Both groups experienced improvement in Ishak activity at week 72, although the improvement rates were higher in non-Latinos than Latinos (59% vs. 47%; $P = 0.03$). For both groups, more patients with SVR compared with non-responders had improved Ishak fibrosis scores. In both groups, baseline Ishak activity score ($P < 0.0001$ for both) was predictive of Ishak activity response. Additional predictors in Latinos were age ($P = 0.0023$), body mass index (BMI) ($P = 0.068$), baseline ALT quotient ($P = 0.031$), and baseline Ishak fibrosis scores ($P = 0.021$). There were no significant differences in steatosis changes between the two groups. Adverse events (AEs) and withdrawals due to AEs were more frequent in non-Latinos. **CONCLUSIONS:** Significant proportions of patients in both groups had histologic response to peginterferon alpha-2a plus ribavirin. However, histologic response was higher in non-Latinos than in Latinos regardless of virologic response. This study highlights the need for additional strategies to improve virologic response in Latinos.

Effectiveness of hepatitis C treatment with pegylated interferon and ribavirin in urban minority patients. Feuerstadt P, Bunim AL, Garcia H, et al. *Hepatology.* 2010 Apr;51(4):1137-43.

Randomized controlled trials of hepatitis C virus (HCV) therapy with pegylated interferon and ribavirin have demonstrated sustained viral response rates (SVRs) of 54%-63% (efficacy). Treatment results in clinical practice (effectiveness) may not be equivalent. The goal of this study was to assess the effectiveness of HCV treatment with pegylated interferon and ribavirin in a treatment-naïve, human immunodeficiency virus (HIV)-negative, United States urban population with many ethnic minority patients. We evaluated 2,370 outpatients for HCV therapy from 2001 to 2006 in the Faculty Practice of the Albert Einstein College of Medicine or the attending-supervised Montefiore Medical Center Liver Clinic. Care was supervised by one experienced physician under conditions of everyday clinical practice, and appropriate ancillary resources were made available to all patients. Two hundred fifty-five patients were treated with a mean age of 50 years (60% male, 40% female; 58% Hispanic, 20% African American, 9% Caucasian, 13% other; 68% genotype 1, the remainder genotypes 2 or 3). Patients had at least one liver biopsy. Intention-to-treat analysis (ITT) showed SVR in 14% of genotype 1 patients and 37% in genotype 2/3 patients ($P < 0.001$). SVR was significantly higher in faculty practice

(27%) than in clinic patients (15%) by intention-to-treat ($P = 0.01$) but not per-protocol analysis (46% faculty practice, 34% clinic). 3.3% of 1,656 treatment-naïve, HIV antibody-negative individuals ultimately achieved SVR. Current hepatitis C therapies may sometimes be unavailable to, inappropriate for, and ineffective in United States urban patients. Treatment with pegylated interferon and ribavirin was less effective in this population than is implied by multinational phase III controlled trials. New strategies are needed to care for such patients.

Distribution of different hepatitis C virus genotypes in patients with hepatitis C virus infection. Bokharaei Salim F, Keyvani H, Amiri A, et al. *World J Gastroenterol.* 2010 Apr 28;16(16):2005-9.

<http://www.ncbi.nlm.nih.gov/pubmed/20419838>

AIM: To investigate the presence of mixed infection and discrepancy between hepatitis C virus (HCV) genotypes in plasma, peripheral blood mononuclear cells (PBMCs), and liver biopsy specimens. **METHODS:** From September 2008 up to April 2009, 133 patients with chronic hepatitis C referred to Firouzgar Hospital for initiation of an antiviral therapy were recruited in the study. Five milliliters of peripheral blood was collected from each patient and liver biopsy was performed in those who gave consent or had indications. HCV genotyping was done using INNO-LiPA(TM) HCV II in serum, PBMCs, and liver biopsy specimens and then confirmed by sequencing of 5'-UTR fragments. **RESULTS:** The mean age of patients was 30.3 +/- 17.1 years. Multiple transfusion was seen in 124 (93.2%) of patients. Multiple HCV genotypes were found in 3 (2.3%) of 133 plasma samples, 9 (6.8%) of 133 PBMC samples, and 8 (18.2%) of 44 liver biopsy specimens. It is notable that the different genotypes found in PBMCs were not the same as those found in plasma and liver biopsy specimens. **CONCLUSION:** Our study shows that a significant proportion of patients with chronic hepatitis C are affected by multiple HCV genotypes which may not be detectable only in serum of patients.

Twelve weeks posttreatment follow-up is as relevant as 24 weeks to determine the sustained virologic response in patients with hepatitis C virus receiving pegylated interferon and ribavirin. Martinot-Peignoux M, Stern C, Maylin S, et al. *Hepatology.* 2010 Apr;51(4):1122-6.

<http://www.ncbi.nlm.nih.gov/pubmed/20069649>

A sustained virologic response (SVR) in patients with chronic hepatitis C receiving pegylated interferon (PEG-IFN) plus ribavirin is defined as undetectable serum HCV-RNA at 24 weeks (W+24) posttreatment follow-up. Viral load outcome in patients with virological relapse (VR) has not been explored. This study evaluated whether the assessment of serum HCV-RNA 12 weeks (W+12) after the end of treatment was as relevant as W+24 to evaluate SVR in 573 patients who received combination PEG-IFN and ribavirin and had a virological response at the end of treatment. Serum HCV-RNA was measured, using a new assay based on transcription-mediated amplification (TMA) with a lowest detection limit of 5-10 IU/mL, at W+12 and W+24 after the end of treatment. VR was defined as reappearance of detectable HCV-RNA at W+24 posttreatment follow-up. The positive predictive value (PPV) of undetectable serum HCV-RNA at W+12 was evaluated to identify patients with SVR, and the viral load outcome was measured in relapse patients. At the W+24 posttreatment follow-up, 408 (71%) patients had an SVR, 181 (71.2%) were treated with PEG-IFNalpha-2a and ribavirin, and 227 (71.1%) were treated with PEG-IFNalpha-2b and ribavirin. At W+12, serum HCV-RNA was undetectable in 409 patients, and 408 patients were SVR (PPV 99.7%, 95% confidence interval 99.1-100). In relapse patients, serum HCV-RNA levels were 5.623 +/- 0.748, 4.979 +/- 0.870, and 5.216 +/- 0.758 log(10)

IU/mL at baseline, W+12, and W+24, respectively. **CONCLUSION:** Our results show that the assessment of serum HCV-RNA 12 weeks after the end of treatment, using the highly sensitive TMA assay (PPV 99.7%), is as relevant as after 24 weeks to predict SVR and make decisions on the management of treated patients, suggesting a new definition for SVR.

Extrahepatic manifestations associated with chronic hepatitis C infections in Poland.

Zarebska-Michaluk DA, Lebensztejn DM, Kryczka WM, Skiba E. Adv Med Sci. 2010 Apr 6:1-7. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20371429>

PURPOSE: To assess the prevalence and predictive factors of extrahepatic manifestation (EM) in patients with chronic hepatitis C (CHC) infection in Poland. **MATERIAL AND METHODS:** 340 consecutive patients (mean age: 42 years) with untreated CHC were studied between 2000 and 2006. The HCV infection was defined by positive serology and serum HCV RNA. The inflammation grade and fibrosis stage were assessed according to Ishak. Demographic, laboratory and liver biopsy data were collected. The patients with liver cirrhosis, concomitant HBV or HIV infection, autoimmune liver diseases and alcohol abusers were excluded from the analysis. **RESULTS:** 210 patients with CHC (61.7%) presented at least 1 extrahepatic manifestation, including mixed cryoglobulinemia (37.1%), thrombocytopenia (27.6%), thyroid autoimmunity (16.2%), dermatological disorders (4.1%) and type 2 diabetes (4.1%). Other EM such as the sicca syndrome, nephropathy, polyneuropathy and B-cell lymphoma were observed in single cases. In multivariate analysis lower platelet count was found as a predictive factor of EM in patients with CHC. **CONCLUSIONS:** The majority of patients with CHC, living in Poland, have EM, of which cryoglobulinemia, thrombocytopenia, thyroid autoimmunity, dermatological disorders and type 2 diabetes are most common. Through the multivariate analysis the lower platelet predicts extrahepatic manifestations associated with chronic hepatitis C.

Hepatocellular carcinoma in individuals with HBV infection or HBV-HCV co-infection in a low endemic country. Davíðsdóttir L, Duberg AS, Törner A, et al. Scand J Gastroenterol. 2010 Apr 12. [Epub ahead of print]

<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.

Hormone therapy in Brazilian postmenopausal women with chronic hepatitis C: a pilot study. Padua MA, Fonseca AM, Deguti MM, et al. *Climacteric*. 2010 Apr;13(2):179-86.

<http://www.ncbi.nlm.nih.gov/pubmed/19657792>

OBJECTIVE: To evaluate liver function and hemostatic parameters in postmenopausal women who have chronic infection with the hepatitis C virus and climacteric symptoms and are undergoing hormone therapy (HT) (standard dose of transdermal continuous combined hormone therapy). **DESIGN:** Fifty out of 336 postmenopausal patients with chronic infection with the hepatitis C virus were selected. The non-inclusion criteria were other chronic or systemic liver diseases, severe vascular diseases, autoimmune diseases or malignant tumors. The patients were randomized into two groups: the HT group with 25 patients to be given transdermal hormone therapy (50 microg estradiol plus 170 microg norethisterone/day) and the control group with the other 25 patients (no medication). Hepatic tests (alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase, total alkaline phosphatase, albumin, serum bilirubin) and hemostatic parameters (prothrombin time, factor V, fibrinogen) were evaluated at baseline and at 1, 4, 7 and 9 months of treatment. **RESULTS:** No significant changes in parameters were found in the comparison between the treated group and the controls, except for a decrease in total alkaline phosphatase ($p = 0.002$), presumably due to changes in bone remodelling. **CONCLUSIONS:** There were no changes in liver function after a 9-month treatment with transdermal estradiol plus norethisterone in symptomatic postmenopausal patients with hepatitis C.

Plasma prohepcidin levels in patients with chronic viral hepatitis: relationship with liver fibrosis. Olmez OF, Gurel S, Yilmaz Y. *Eur J Gastroenterol Hepatol*. 2010 Apr;22(4):461-5.

<http://www.ncbi.nlm.nih.gov/pubmed/19940783>

OBJECTIVES: Iron is deemed to play a crucial role in the pathophysiology of liver damage in patients with chronic viral hepatitis. Hepsidin has recently emerged as the key hormone in the regulation of iron balance and recycling. We assessed plasma prohepcidin levels in patients with chronic viral hepatitis and investigated the association of this molecule with iron parameters, histologic activity index, and liver fibrosis scores. **METHODS:** We enrolled 35 patients with chronic hepatitis C, 27 with chronic hepatitis B, and 21 healthy controls. Plasma levels of prohepcidin were measured by enzyme-linked immunosorbent assay. **RESULTS:** Mean prohepcidin levels were significantly lower in patients with chronic hepatitis B than in those with chronic hepatitis C ($P < 0.001$) and healthy comparison controls ($P < 0.05$). In patients with chronic hepatitis C, prohepcidin was independently associated with liver fibrosis scores (beta=-0.009, standard error=0.003, $P < 0.05$). No association of prohepcidin with iron parameters was found. **CONCLUSION:** Significantly lower prohepcidin levels are frequently found in patients with chronic hepatitis B. Levels of this molecule may represent a biochemical correlate of fibrosis in chronic hepatitis C virus infection.

Disease progression from chronic hepatitis C to cirrhosis and hepatocellular carcinoma is associated with repression of interferon regulatory factor-1. Zekri AR, Moharram RA, Mohamed WS, et al. Eur J Gastroenterol Hepatol. 2010 Apr;22(4):450-6.

<http://www.ncbi.nlm.nih.gov/pubmed/19858727>

BACKGROUND/AIM: Infection with hepatitis C virus (HCV) frequently results in a persistent infection, suggesting that it has evolved efficient mechanism(s) for blocking the host cell's innate antiviral response. The immune response to virus infection results in activation or direct induction of the interferon regulatory factors (IRFs), which are a family of proteins involved in the regulation of interferon (IFN) and IFN inducible genes. IRF-3 and IRF-7 have been shown to play an essential role in virus-dependent signaling, whereas IRF-1 is critical for proper IFN-dependent gene expression. This study has been performed to show the expression profile of IRF-1, IRF-3, and IRF-7 in Egyptian patients with HCV-related liver diseases and hepatocellular carcinoma (HCC). **MATERIALS AND METHODS:** This study included 90 patients, who were positive for HCV infection by reverse transcription PCR, divided into three groups: group I (Gr I) included 30 patients with chronic hepatitis C, group II (Gr II) included 30 patients with liver cirrhosis in addition to group III (Gr III) of 30 patients with HCC. Reverse transcription PCR analysis was performed to determine the expression profile of IRF-1, IRF-3, and IRF-7 genes extracted from the peripheral blood mononuclear cells of those patients. **RESULTS:** IRF-1 expression was significantly higher ($P < 0.001$) in patients of Gr I (86.6%) compared with those in Gr II (46.7%) and Gr III (36.7%), whereas IRF-3 expression was significantly higher ($P < 0.005$) among patients of Gr II (73.3%) in comparison with that in Gr I (50%) and Gr III (36.7%). In contrast, although expression of IRF-7 was higher in Gr II than in the other groups, there was no statistically significant difference ($P > 0.05$). **CONCLUSION:** Alterations in IRFs expression might be considered as markers associated with a higher risk of cirrhosis in patients with chronic HCV infection. Expression of IRF-1 and IRF-3 were more prevalent in patients with chronic HCV and cirrhosis, respectively, in comparison with HCC patients. Thus, IRF-1 could be nominated as one of the tumor suppressor factors and could aid in the early detection of HCC.

Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C Trial. Seeff LB, Everson GT, Morgan TR, et al. Clin Gastroenterol Hepatol. 2010 Apr 1. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20362695>

BACKGROUND & AIMS: Although percutaneous liver biopsy is a standard diagnostic procedure, it has drawbacks, including risk of serious complications. It is not known whether persons with advanced chronic liver disease have a greater risk of complications from liver biopsy than patients with more mild, chronic liver disease. The safety and complications of liver biopsy were examined in patients with hepatitis C-related bridging fibrosis or cirrhosis who were enrolled in the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis trial. **METHODS:** Standard case report forms from 2740 liver biopsies performed at 10 study sites between 2000 and 2006 were reviewed for serious adverse events, along with information from questionnaires completed by investigators about details of biopsy techniques used at each hospital. **RESULTS:** There were 29 serious adverse events (1.1%); the most common was bleeding (16 cases; 0.6%). There were no biopsy-related deaths. The bleeding rate was higher among patients with platelet counts of 60,000/mm³ or less and among those with an international normalized ratio of 1.3 or greater, although none of the patients with an international normalized ratio greater than 1.5 bled.

Excluding subjects with a platelet count of 60,000/mm³ or less would have reduced the bleeding rate by 25% (4 of 16), eliminating only 2.8% (77 of 2740) of biopsies. Operator experience, the type of needle used, or the performance of the biopsy under ultrasound guidance did not influence the frequencies of adverse events. **CONCLUSIONS:** Approximately 0.5% of persons with hepatitis C and advanced fibrosis experienced potentially serious bleeding after liver biopsy; risk increased significantly in patients with platelet counts of 60,000/mm³ or less.

High rates of sustained virological response in hepatitis C virus-infected injection drug users receiving directly observed therapy with peginterferon alpha-2a (40KD) (PEGASYS) and once-daily ribavirin. Waizmann M, Ackermann G. *J Subst Abuse Treat.* 2010

Jun;38(4):338-45. Epub 2010 Apr 1.

<http://www.ncbi.nlm.nih.gov/pubmed/20362408>

This retrospective study evaluated the efficacy and tolerability of directly observed therapy with peginterferon alfa-2a and once-daily ribavirin (RBV) for chronic hepatitis C in 49 opioid-addicted injection drug users (IDUs) participating in a drug treatment program at a specialized outpatient center. Patients also received prophylactic citalopram to minimize the risk of interferon-induced depression. Patients had daily access to and support from specialist physicians, nurses and counseling services at the center, and a 24-hour helpline. Sustained virological response was achieved by 48 of 49 patients (98%) overall, including 20 of 21 (95%) hepatitis C virus (HCV) Genotype 1/4-infected patients and 28 of 28 (100%) Genotype 2/3-infected patients. Treatment was well tolerated, and no unexpected side effects of peginterferon treatment were seen. The safety profile of once-daily RBV was not different from twice-daily dosing. Decline in hemoglobin levels was similar to those reported in clinical trials including once-daily RBV and did not lead to dose reduction or treatment withdrawal. **Our data demonstrate** that HCV-infected IDUs on stable L-polamidone (methadone) or buprenorphine maintenance can be successfully and safely treated with peginterferon alfa-2a and RBV in an optimal substitution setting.

Low vitamin D serum level is related to severe fibrosis and low responsiveness to interferon-based therapy in genotype 1 chronic hepatitis C. Petta S, Cammà C, Scazzone C, et al. *Hepatology.* 2010 Apr;51(4):1158-67.

<http://www.ncbi.nlm.nih.gov/pubmed/20162613>

25-Hydroxyvitamin D (25[OH]D) can potentially interfere with inflammatory response and fibrogenesis. Its role in disease progression in chronic hepatitis C (CHC) and its relation with histological and sustained virological response (SVR) to therapy are unknown. One hundred ninety-seven patients with biopsy-proven genotype 1 (G1) CHC and 49 healthy subjects matched by age and sex were consecutively evaluated. One hundred sixty-seven patients underwent antiviral therapy with pegylated interferon plus ribavirin. The 25(OH)D serum levels were measured by high-pressure liquid chromatography. Tissue expression of cytochrome (CY) P27A1 and CYP2R1, liver 25-hydroxylating enzymes, were assessed by immunohistochemistry in 34 patients with CHC, and in eight controls. The 25(OH)D serum levels were significantly lower in CHC than in controls (25.07 +/- 9.92 microg/L versus 43.06 +/- 10.19; P < 0.001). Lower levels of 25(OH)D were independently linked to female sex (P = 0.007) and necroinflammation (P = 0.04) by linear regression analysis. CYP27A1, but not CYP2R1, was directly related to 25(OH)D levels (P = 0.01), and inversely to necroinflammation (P = 0.01). Low 25(OH)D (odds ratio [OR], 0.942; 95% confidence interval [CI], 0.893-0.994) and cholesterol (OR, 0.981; 95% CI,

0.969-0.992) levels, older age (OR, 1.043; 95%CI, 1.002-1.085), high ferritin (OR, 1.003; 95%CI, 1.001-1.005), and necroinflammation (OR, 2.235; 95%CI, 1.014-4.929) were independently associated with severe fibrosis (F3-F4) by multivariate logistic analysis. Seventy patients (41%) achieved SVR. By multivariate analysis, hepatic steatosis (OR, 0.971; 95%CI, 0.944-0.999), lower cholesterol (OR, 1.009; 95% CI, 1.000-1.018), and 25(OH)D levels (OR, 1.039; 95%CI, 1.002-1.077) were independently associated with no SVR. **CONCLUSION:** G1 CHC patients had low 25(OH)D serum levels, possibly because of reduced CYP27A1 expression. Low vitamin D is linked to severe fibrosis and low SVR on interferon (IFN)-based therapy.

Hepatobiliary function assessed by 99mTc-mebrofenin cholescintigraphy in the evaluation of fibrosis in chronic hepatitis: histopathological correlation. Kula M, Karacavus S, Baskol M, et al. Nucl Med Commun. 2010 Apr;31(4):280-5.

<http://www.ncbi.nlm.nih.gov/pubmed/20087241>

PURPOSE: Although liver biopsy remains the gold standard in the staging of liver fibrosis in chronic hepatitis C virus (HCV) infection, several noninvasive methods are under evaluation for clinical use. The aim of this study was to evaluate the utility of hepatobiliary function through technetium-99m-N-(-3-bromo-2,4,6-trimethylacetanilide) iminodiacetic acid (Tc-mebrofenin) scintigraphy in evaluating liver fibrosis in patients with chronic HCV infection. **METHODS:** We studied 62 patients with HCV (18 men, 44 women). The patients were allocated into three groups according to histopathological score: group 1: portal/periportal fibrosis (21 patients; eight men, 13 women); group 2: bridging fibrosis (23 patients; seven men, 16 women); and group 3: incomplete/complete cirrhosis (18 patients; three men, 15 women). As a control group, 20 healthy volunteers (six men and 14 women) were studied. Hepatocyte mebrofenin uptake rate, the time required for maximal hepatic activity (Tmax), and the time required for peak activity to decrease by 50% (T1/2max) were calculated using Tc-mebrofenin cholescintigraphy. Scintigraphic parameters were correlated with biochemical parameters and liver histopathology. **RESULTS:** The uptake rates were significantly decreased in all groups with fibrosis compared with the controls (P<0.05). The correlation between the severity of fibrosis and Tc-mebrofenin uptake rate was strongly significant (r=-0.81, P<0.0001). Tmax and T1/2max were significantly prolonged in groups 2 and 3 compared with the controls. Histopathology score was correlated moderately with Tmax and T1/2max (r=0.61, P<0.0001 and r=0.52, P<0.0001, respectively). **CONCLUSION:** The assessment of hepatobiliary function by Tc-mebrofenin scintigraphy may be a good choice for assessing the severity of liver fibrosis in patients with HCV.

Outcome of a hepatitis C outbreak among patients in a pain management clinic. Fazili J, Mallonee S, Tierney WM, et al. Dig Dis Sci. 2010 Apr 22. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20411419>

BACKGROUND AND AIMS: The aims of this study are to evaluate the natural history and response to therapy of patients following a hepatitis C outbreak in a pain management clinic. **METHODS:** A retrospective cohort study was conducted on patients who acquired hepatitis C virus (HCV) at a pain management clinic. Medical records were retrospectively reviewed for 77% of patients with hepatitis C included in the outbreak to obtain data regarding laboratory results, treatment, and outcomes. Chi-square, Fisher's exact, and Student's t-test were used to determine variables that were significantly associated with spontaneous clearance or sustained virologic response to therapy. **RESULTS:** Fifty Caucasian patients (31 women, 19 men; mean

age 52 years) were included. Eleven of 50 (22%) patients cleared HCV spontaneously (clearers). The mean age of clearers was 47 years as compared with 57 years for nonclearers ($P = 0.04$). Liver biopsies were obtained by treating gastroenterologists in 31 patients with mean grade and stage of 2.1 and 1.7, respectively. Gastroenterologists treated 31 of 39 patients with pegylated interferon and ribavirin after a median of 354 (range 140-1,099) days post exposure. Sustained viral response (SVR) was observed in 65% (20/31) on an intention-to-treat basis. In patients who completed therapy, 91% (20/22) achieved SVR. Age, sex, weight, pretreatment alanine aminotransferase (ALT), and histologic parameters were not associated with SVR.

CONCLUSIONS: In this large cohort of US immunocompetent patients with recent HCV infection, 22% resolved spontaneously. Younger age was the only predictor of spontaneous clearance. In patients with early chronic HCV, 65% achieved SVR.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Soluble angiogenesis factors in sera of Egyptian patients with hepatitis C virus infection: correlation with disease severity. Talaat RM. *Viral Immunol.* 2010 Apr;23(2):151-7.

<http://www.ncbi.nlm.nih.gov/pubmed/20373995>

Hepatitis C virus (HCV) infection causes chronic hepatitis, which gradually progresses to liver cirrhosis and subsequently to hepatocellular carcinoma (HCC). Angiogenesis plays a major role in chronic inflammation and may have prognostic value in disease progression. This study was designed to evaluate vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and tumor necrosis factor-alpha (TNF-alpha) as prognostic factors of disease progression in Egyptian patients with different stages of HCV-related cirrhosis and HCC. VEGF, PDGF, and TNF-alpha were measured using enzyme-linked immunosorbent assay (ELISA) in 82 HCV-infected patients (20 mild, 20 moderate, and 20 severe cirrhosis patients, and 22 HCC patients), and 20 healthy controls. Our results showed comparable increases in VEGF and PDGF levels in those with increasing clinical stages of disease, with maximal production seen in HCC patients. A gradual elevation of TNF-alpha levels was seen also in HCV-infected patients at different stages of disease and HCC. A statistically significantly positive correlation between serum levels of VEGF, PDGF, and TNF-alpha, and grade of disease was recorded. **Thus** assessment of these parameters in those with different stages of disease may be helpful in choosing the best treatment strategy, and indicate that anti-angiogenic therapy may be useful.

Natural epitope variants of the hepatitis C virus impair cytotoxic T lymphocyte activity.

Wang S, Buchli R, Schiller J, et al. *World J Gastroenterol.* 2010 Apr 28;16(16):1953-69.

<http://www.ncbi.nlm.nih.gov/pubmed/20419832>

AIM: To understand how interactions between hepatitis C virus (HCV) and the host's immune system might lead to viral persistence or effective elimination of HCV. **METHODS:** Nucleotides 3519-3935 of the non-structural 3 (NS3) region were amplified by using reverse transcription polymerase chain reaction (PCR). PCR products of the HCV NS3 regions were integrated into a PCR((R)) T7TOPO((R)) TA vector and then sequenced in both directions using an automated DNA sequencer. Relative major histocompatibility complex binding levels of wild-type and variant peptides were performed by fluorescence polarization-based peptide competition assays. Peptides with wild type and variant sequences of NS3 were synthesized locally using F-moc chemistry and purified by high-performance liquid chromatography. Specific cytotoxic T lymphocytes (CTLs) clones toward HCV NS3 wild-type peptides were

generated through limiting dilution cloning. The CTL clones specifically recognizing HCV NS3 wild-type peptides were tested by tetramer staining and flow cytometry. Cytolytic activity of CTL clones was measured using target cells labeled with the fluorescence enhancing ligand, DELFIA EuTDA. **RESULTS:** The pattern of natural variants within three human leukocyte antigen (HLA)-A2-restricted NS3 epitopes has been examined in one patient with chronic HCV infection at 12, 28 and 63 mo post-infection. Results obtained may provide convincing evidence of immune selection pressure for all epitopes investigated. Statistical analysis of the extensive sequence variation found within these NS3 epitopes favors a Darwinian selection model of variant viruses. Mutations within the epitopes coincided with the decline of CTL responses, and peptide-binding studies suggested a significant impact of the mutation on T cell recognition rather than peptide presentation by HLA molecules. While most variants were either not recognized or elicited low responses, such could antagonize CTL responses to target cells pulsed with wild-type peptides. **CONCLUSION:** Cross-recognition of CTL epitopes from wild-type and naturally-occurring HCV variants may lead to impaired immune responses and ultimately contribute to viral persistence.

Consistent beneficial effects of killer cell immunoglobulin-like receptor 2DL3 and group 1 human leukocyte antigen-C following exposure to hepatitis C virus. Knapp S, Warshaw U, Hegazy D, et al. *Hepatology*. 2010 Apr;51(4):1168-75.

<http://www.ncbi.nlm.nih.gov/pubmed/20077564>

Natural killer cells are a key component in the immune control of viral infections. Their functions are controlled by inhibitory receptors for major histocompatibility complex (MHC) class I, including the killer cell immunoglobulin-like receptors (KIR). KIR2DL3 in combination with its cognate human leukocyte antigen (HLA)-C ligand has been shown to be associated with spontaneous resolution of viremia following hepatitis C virus (HCV) infection. In order to determine if this gene combination is advantageous across all potential outcomes following HCV exposure, we studied individuals with apparent resistance to HCV infection who remain seronegative and aviremic despite long-term injection drug use and also individuals chronically infected with HCV who successfully clear HCV with treatment. Homozygosity for KIR2DL3 in combination with group 1 HLA-C allotypes was more frequent in exposed seronegative aviremic individuals as compared to those with chronic HCV (25.0% versus 9.7%, $P = 0.003$, odds ratio [OR] = 3.1, 95% confidence interval [CI] = 1.3-7.1) in a model similar to that found for those spontaneously resolving HCV. In individuals undergoing treatment for HCV, those with KIR2DL3 and group 1 HLA-C were more likely to make a sustained virological response (SVR) ($P = 0.013$, OR = 2.3, 95% CI = 1.1-4.5). KIR and HLA-C protection in both treatment response and spontaneously resolving HCV was validated at the allelic level, in which KIR2DL3-HLA-Cw*03 was associated with SVR ($P = 0.004$, OR = 3.4, 95% CI = 1.5-8.7) and KIR2DL3/KIR2DL3-HLA-Cw*03 was associated with spontaneous resolution of HCV infection ($P = 0.01$, OR = 2.3, 95% CI = 1.2-4.4). Conclusion: KIR and HLA-C genes are consistently beneficial determinants in the outcome of HCV infection. This advantage extends to the allelic level for both gene families.

Cyclic sulfones as novel P3-caps for hepatitis C virus NS3/4A (HCV NS3/4A) protease inhibitors: synthesis and evaluation of inhibitors with improved potency and pharmacokinetic profiles. Velázquez F, Sannigrahi M, Bennett F, et al. *J Med Chem.* 2010 Apr 22;53(8):3075-85.

<http://www.ncbi.nlm.nih.gov/pubmed/20302300>

HCV infection affects more than 170 million people worldwide and many of those patients will reach the end stage complications of the disease which include hepatocarcinoma and liver failure. The success rate for treatment of patients infected with genotype-1 is about 40%. Therefore, novel treatments are needed to combat the infection. The HCV NS3 protease inhibitor Boceprevir (1) was reported by our research group and efforts continue for the discovery of more potent compounds with improved pharmacokinetic profiles. A new series of HCV NS3 protease inhibitors having a cyclic sulfone P3-cap have been discovered. Compounds 43 and 44 showed $K(i)^*$ values in the single-digit nM range and their cellular potency was improved by 10-fold compared to 1. The pharmacokinetic profiles of 43 and 44 in rats and monkeys were also improved to achieve higher plasma levels after oral administration.

The protease domain increases the translocation stepping efficiency of the hepatitis C virus NS3-4A helicase. Rajagopal V, Gurjar M, Levin MK, Patel SS. *J Biol Chem.* 2010 Apr 2. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20363755>

Hepatitis C virus NS3 protein has two enzymatic activities of helicase and protease that are essential for viral replication. The helicase separates the strands of DNA and RNA duplexes using the energy from ATP hydrolysis. To understand how ATP hydrolysis is coupled to helicase movement, we measured the single turnover helicase translocation-dissociation kinetics and the pre-steady-state P_i -release kinetics on single-stranded RNA and DNA substrates of different lengths. The parameters of stepping were determined from global fitting of the two types of kinetic measurements into a computational model that describes translocation as a sequence of coupled hydrolysis-stepping reactions. Our results show that the HCV helicase moves with a faster rate on single stranded RNA than on DNA. The HCV helicase steps on the RNA or DNA one nucleotide at a time, and due to imperfect coupling, not every ATP hydrolysis event produces a successful step. Comparison of the helicase domain (NS3h) with the protease-helicase (NS3-4A) shows that the most significant contribution of the protease domain is to improve the translocation stepping efficiency of the helicase. While for NS3h, only 20% of the hydrolysis events result in translocation, the coupling for NS3-4A is near-perfect 93%. The presence of the protease domain also significantly reduces the stepping rate, but it doubles the processivity. These effects of the protease domain on the helicase can be explained by an improved allosteric cross-talk between the ATP- and nucleic acid- binding sites achieved by the overall stabilization of the helicase domain structure.

A small molecule inhibits HCV replication and alters NS4B's subcellular distribution.

Bryson PD, Cho NJ, Einav S, et al. *Antiviral Res.* 2010 Apr 2. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20363257>

Hepatitis C Virus (HCV) is a leading cause of liver disease and represents a significant public health challenge. Treatments for this disease are inadequate and improved antiviral therapies are necessary. Several such antivirals are in development, most of which target the well-characterized NS3 protease or the NS5B polymerase. In contrast, the nonstructural 4B (NS4B)

protein, though essential for HCV RNA replication, has been the subject of few pharmacological studies. One of the functions ascribed to this protein is the ability to form intracellular membrane-associated foci (MAF), which are believed to be related to the sites of viral replication. Here, we report the identification of a small molecule that inhibits HCV replication and disrupts the organization of these MAF. Genetic analysis links the compound's mode of action to the NS4B gene product, and transient transfections of NS4B-GFP demonstrate that treatment with this compound can lead to the formation of novel elongated assemblies of NS4B. Furthermore, an in vitro dynamic light scattering assay provides evidence that the second amphipathic helix of NS4B maybe the target of the drug. **Our results demonstrate** that this molecule represents a new potential class of HCV inhibitors and also provides us with a useful tool for studying the HCV life cycle.

Cleavage of mitochondrial antiviral signaling protein in the liver of patients with chronic hepatitis C correlates with a reduced activation of the endogenous interferon system.

Bellecave P, Sarasin-Filipowicz M, et al. *Hepatology*. 2010 Apr;51(4):1127-36.

<http://www.ncbi.nlm.nih.gov/pubmed/20044805>

Hepatitis C virus (HCV) infection induces the endogenous interferon (IFN) system in the liver in some but not all patients with chronic hepatitis C (CHC). Patients with a pre-activated IFN system are less likely to respond to the current standard therapy with pegylated IFN-alpha. Mitochondrial antiviral signaling protein (MAVS) is an important adaptor molecule in a signal transduction pathway that senses viral infections and transcriptionally activates IFN-beta. The HCV NS3-4A protease can cleave and thereby inactivate MAVS in vitro, and, therefore, might be crucial in determining the activation status of the IFN system in the liver of infected patients. We analyzed liver biopsies from 129 patients with CHC to investigate whether MAVS is cleaved in vivo and whether cleavage prevents the induction of the endogenous IFN system. Cleavage of MAVS was detected in 62 of the 129 samples (48%) and was more extensive in patients with a high HCV viral load. MAVS was cleaved by all HCV genotypes (GTs), but more efficiently by GTs 2 and 3 than by GTs 1 and 4. The IFN-induced Janus kinase (Jak)-signal transducer and activator of transcription protein (STAT) pathway was less frequently activated in patients with cleaved MAVS, and there was a significant inverse correlation between cleavage of MAVS and the expression level of the IFN-stimulated genes IFI44L, Viperin, IFI27, USP18, and STAT1. We conclude that the pre-activation status of the endogenous IFN system in the liver of patients with CHC is in part regulated by cleavage of MAVS.

Core-specific adaptive regulatory T-cells in different outcomes of hepatitis C. Langhans B, Braunschweiger I, Arndt S, et al. *Clin Sci (Lond)*. 2010 Apr 20;119(2):97-109.

<http://www.ncbi.nlm.nih.gov/pubmed/20222873>

CD4⁺ Treg-cells (regulatory T-cells) probably contribute to the impaired virus-specific T-cell responses in chronic HCV (hepatitis C virus) infection; however, their antigen-specificity has remained elusive. In the present study, we analysed peripheral blood CD4⁺ Treg-cells in patients with chronic hepatitis C and subjects with self-limited HCV infection and characterized individual Treg-cell clones obtained from both groups at the phenotypic and functional level. Foxp3 (forkhead box p3)⁺CD25⁺CD4⁺ Treg-cells were detected more frequently in patients with chronic hepatitis C than self-limited HCV infection, which responded to HCV core stimulation and inhibited proliferation of reporter cells. Cloning under limiting dilution conditions resulted in 14 and six hypoproliferative Foxp3⁺CD25⁺CD127⁻CD4⁺ T-cell clones

from patients with chronic hepatitis C and subjects with self-limited HCV infection respectively. All clones expressed Treg-cell markers and produced IL (interleukin)-10 upon mitogen stimulation. However, exclusively Treg-cell clones from chronic hepatitis C produced IL-10 in response to HCV core and inhibited proliferation of reporter T-cells. These core-specific Treg-cell clones recognized epitopes in two regions of HCV core (amino acids 1-44 and 79-113). Co-culture inhibition assays demonstrated Treg-cells to inhibit reporter T-cells via secretion of IL-10 and IL-35 rather than cell-contact-dependent mechanisms. Finally, the HCV-specific Treg-cell clones lost their functional capacity, along with Foxp3 expression, if kept in culture without HCV core exposure. In conclusion, we identified functionally active HCV core-specific Treg-cells in patients with chronic hepatitis C, which share their epitopes with conventional T-cells and require the continued presence of antigen to maintain their functional differentiation. Thus HCV core-specific Treg-cells may contribute to the immunoregulatory balance in chronic hepatitis C.

Amino acid substitutions in the hepatitis C virus core region of genotype 1b affect very early viral dynamics during treatment with telaprevir, peginterferon, and ribavirin. Akuta N, Suzuki F, Hirakawa M, et al. J Med Virol. 2010 Apr;82(4):575-82.

<http://www.ncbi.nlm.nih.gov/pubmed/20166188>

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 rate of HCV RNA loss following 12-week triple therapy, and determine the effect of aa substitutions on very early (within 48 hr) viral dynamics. Sixty-seven patients infected with HCV genotype 1b (HCV-1b) and high viral load who received 12-week triple therapy were studied. RNA loss could be achieved in 2%, 34%, 80%, 92%, 95%, 94%, and 90% of the patients after 1, 2, 4, 6, 8, 10, and 12 weeks of triple therapy, respectively. After 24-hr treatment, the proportion of patients with Arg70 and Leu91 substitutions with ≥ 3.0 log fall in HCV RNA was significantly higher than those with < 3.0 log fall ($P = 0.008$). However, the aa substitution patterns in the core region did not influence the fall in HCV RNA after 48-hr treatment. Multivariate analysis identified substitutions of aa 70 and 91 ($P = 0.014$) and level of viremia at baseline (≥ 7.0 log IU/ml; $P = 0.085$) as independent parameters that determined the ≥ 3.0 log fall in HCV RNA level after 24-hr triple therapy. It is concluded that 12-week triple therapy achieved high rates of loss of HCV RNA in Japanese patients infected with HCV-1b and high viral load, and that the aa substitution pattern in the core region seems to influence very early viral dynamics.

CXC chemokine ligand 4 (Cxcl4) is a platelet-derived mediator of experimental liver fibrosis. Zaldivar MM, Pauels K, von Hundelshausen P, et al.

<http://www.ncbi.nlm.nih.gov/pubmed/20162727>

Liver fibrosis is a major cause of morbidity and mortality worldwide. Platelets are involved in liver damage, but the underlying molecular mechanisms remain elusive. Here, we investigate the platelet-derived chemokine (C-X-C motif) ligand 4 (CXCL4) as a molecular mediator of fibrotic liver damage. Serum concentrations and intrahepatic messenger RNA of CXCL4 were measured in patients with chronic liver diseases and mice after toxic liver injury. Platelet aggregation in early fibrosis was determined by electron microscopy in patients and by immunohistochemistry in mice. Cxcl4(-/-) and wild-type mice were subjected to two models of chronic liver injury

(CCl(4) and thioacetamide). The fibrotic phenotype was analyzed by histological, biochemical, and molecular analyses. Intrahepatic infiltration of immune cells was investigated by fluorescence-activated cell sorting, and stellate cells were stimulated with recombinant Cxcl4 in vitro. The results showed that patients with advanced hepatitis C virus-induced fibrosis or nonalcoholic steatohepatitis had increased serum levels and intrahepatic CXCL4 messenger RNA concentrations. Platelets were found directly adjacent to collagen fibrils. The CCl(4) and thioacetamide treatment led to an increase of hepatic Cxcl4 levels, platelet activation, and aggregation in early fibrosis in mice. Accordingly, genetic deletion of Cxcl4 in mice significantly reduced histological and biochemical liver damage in vivo, which was accompanied by changes in the expression of fibrosis-related genes (Timp-1 [tissue inhibitor of matrix metalloproteinase 1], Mmp9 [matrix metalloproteinase 9], Tgf-beta [transforming growth factor beta], IL10 [interleukin 10]). Functionally, Cxcl4(-/-) mice showed a strongly decreased infiltration of neutrophils (Ly6G) and CD8(+) T cells into the liver. In vitro, recombinant murine Cxcl4 stimulated the proliferation, chemotaxis, and chemokine expression of hepatic stellate cells. Conclusion: The results underscore an important role of platelets in chronic liver damage and imply a new target for antifibrotic therapies.

Positive selection of core 70Q variant genotype 1b hepatitis c virus strains induced by pegylated interferon and ribavirin. Kurbanov F, Tanaka Y, Matsuura K, et al. *J Infect Dis.* 2010 Apr 26. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20420509>

BACKGROUND: Approximately 20% of patients with hepatitis C virus (HCV) genotype 1b infection have nonresponse to the most current treatment, pegylated interferon with ribavirin. Mutations in the HCV core region were recently proposed to be associated with nonresponse. Our aim was to evaluate the viral factors associated with treatment failure. **METHODS:** HCV variants were determined directly and after cloning in 66 HCV-1b-infected Japanese patients and in 5 urokinase-type plasminogen activator transgenic severe combined immunodeficiency mice with human hepatocytes (chimeric mice), at baseline, during treatment, and after treatment. **RESULTS:** At baseline, glutamine at position 70 of the HCV core protein (70Q) was detected by direct sequencing in 20% of patients with virologic response and in 43.8% of patients with nonresponse. Among patients with nonresponse, who were examined during and after treatment, the prevalence of the 70Q substitution increased to 56.3%, which indicates that treatment-induced selection occurred in all patients with nonresponse who had 70Q quasispecies detectable by cloning. This observation was reinforced by the results from experimentally infected chimeric mice. Logistic regression analysis indicated that detection of 70Q quasispecies was associated with a statistically significantly increased risk of nonresponse (odds ratio, 15.1; [Formula: see text]) in the studied cohort. **CONCLUSION:** Presence of the 70Q quasispecies at baseline was associated with an increased risk of treatment failure, as indicated by the positive selection of the 70Q clones induced by treatment with pegylated interferon with ribavirin. These results urge further investigation of the mechanisms of this association.

HIV/HCV COINFECTION

Clearance of hepatitis C virus RNA from serum in HIV/hepatitis C virus coinfection indicates eradication from peripheral blood mononuclear cells. Page EE, Cox A, Atkins M, Nelson MR. *AIDS.* 2010 Apr 9. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20386424>

OBJECTIVES: The objectives of this study are to determine the frequency of hepatitis C virus (HCV) RNA persistence in peripheral blood mononuclear cells (PBMCs) of HIV-positive patients with clearance of the virus from serum and to identify the presence of any ongoing replication. **DESIGN:** This is a prospective cross-sectional study. **METHODS:** HIV antibody-positive individuals with previous exposure to HCV, but not current infection with HCV, were recruited. Blood was taken to allow identification of HCV RNA in both serum and PBMCs. Intracellular HCV was extracted using the QIAamp RNA Blood MiniKit. Reverse transcriptase-PCR was performed using a modification of the COBAS TaqMan HCV Test for use with the high pure system. **RESULTS:** Twenty-six HIV-positive individuals were recruited to the study. All had previously been infected with HCV. Six individuals had spontaneously cleared HCV, 10 had achieved sustained virological response following 24 weeks of pegylated interferon and ribavirin for acute HCV, and 10 had achieved sustained virological response following standard pegylated interferon and ribavirin therapy for chronic HCV. None demonstrated HCV RNA persistence in either serum or PBMCs. **CONCLUSION:** Our findings lend support to the view that clearance of HCV RNA from serum in HIV/HCV coinfection indicates eradication from PBMCs. Thus, absence of serum HCV RNA 6 months after the end of therapy can be used as a marker of treatment success for interferon-based therapies. However, the advent of small molecule HCV inhibitors may require us to rethink our definitions of response and cure.

Hepatitis C virus RNA detection in different semen fractions of HCV/HIV-1 co-infected men by nested PCR. Savasi V, Parrilla B, Ratti M, Oneta M, Clerici M, Ferrazzi E. Eur J Obstet Gynecol Reprod Biol. 2010 Apr 9. [Epub ahead of print]

<http://www.ncbi.nlm.nih.gov/pubmed/20382466>

OBJECTIVE: The aim was to evaluate, by nested PCR, the prevalence of hepatitis C virus (HCV) RNA in seminal plasma in different semen fractions of HCV/HIV-1 co-infected men. **STUDY DESIGN:** This study enrolled 16 HCV/HIV-1 infected men. A total of 16 seminal samples and 16 blood samples were tested for the presence of HCV-RNA. HCV-RNA in blood plasma was quantified by Amplicor HCV Monitor Test version 2.0 and HCV-RNA detection in seminal plasma, non-spermatozoa cells (NSCs), spermatozoa pellet and swim-up was investigated by nested PCR. **RESULTS:** Thirteen blood plasma samples were positive for HCV-RNA. HCV-RNA was detectable in seminal plasma and in non-sperm cells, but not detectable in spermatozoa samples, neither before nor after swim-up. One of the two patients whose seminal plasma tested positive at nested PCR had undetectable HCV virus in blood plasma. **CONCLUSIONS:** HCV-RNA can be found in seminal plasma and non-sperm cells but not in spermatozoa before and after swim-up. We observed HCV-RNA in the semen of an aviremic man. According to these findings we suggest that sperm washing should be performed for each semen sample of HCV patients before assisted reproduction techniques.

Ability of treatment week 12 viral response to predict long-term outcome in genotype 1 hepatitis C virus/HIV coinfecting patients. Van den Eynde E, Tiraboschi JM, Tural C, et al. AIDS. 2010 Apr 24;24(7):975-82.

<http://www.ncbi.nlm.nih.gov/pubmed/20299963>

OBJECTIVE: Guidelines recommendation to extend treatment duration in genotype 1 hepatitis C virus (HCV)/HIV-coinfecting patients who clear the virus later than treatment week 4 is not evidence-based. Our main objective was to study the ability of week 12 viral response [early

virologic response (EVR)] to predict long-term outcome in patients treated for 48 weeks.

DESIGN: Multicenter retrospective cohort analysis. **METHODS:** Genotype 1 HCV treatment-naive, HIV-coinfected adult patients with compensated liver disease who started combination therapy with fixed-dose pegylated-interferon (pegIFN) alfa-2a or weight-based pegIFN alfa-2b plus ribavirin were included. Univariate and forward stepwise logistic regression analysis were used to identify predictors of sustained viral response (SVR) and relapse. **RESULTS:** By intention-to-treat analysis, 31.3% (87/278) of patients achieved an SVR. SVR rate was more than three-fold higher in patients who cleared the virus by week 12 of treatment compared with late responders. Among 123 end-of-treatment responders, 36 (29.3%) relapsed. Relapse risk increased in patients with cirrhosis, in those with ribavirin dose reductions and in late responders: more than 65% of patients who cleared the virus between weeks 12 and 24 relapsed following 48 weeks of treatment compared with 10% of those attaining a complete EVR (<15 IU/ml) at treatment week 12 (risk ratio 6.4, 95% confidence interval 2.9-14.4). **CONCLUSION:** Viral response at treatment week 12 is a strong predictor of long-term outcome. Genotype 1 HCV/HIV-coinfected patients who achieve a complete EVR (<15 IU/ml) are at low risk of viral relapse after completing the standard 48 weeks of therapy.

Hepatitis C infection on immune recovery in HIV-positive patients on successful HAART: the role of genotype 3. Seminari E, Tinelli C, Ravasi G, et al. *Curr HIV Res.* 2010 Apr 1;8(3):186-93.

<http://www.ncbi.nlm.nih.gov/pubmed/20163342>

OBJECTIVE: The primary objective of this study was to investigate the impact of HCV infection and of HCV genotypes on immune restoration in HIV-infected patients on a successful HAART regimen. **METHODS:** Patients from the MASTER Study were included in this current longitudinal study if they met the following criteria: being on any successful HAART, availability of CD4+ cell count and HIV RNA level before starting the suppressive HAART and 12 months after suppressive therapy, availability of HCV antibodies. The primary endpoints of the study were defined as achieving a difference above 100 cell/mm³ between CD4+ at baseline and at time of HIV RNA suppression while on therapy (DeltaCD4+early), or 12 month after a suppressive therapy (DeltaCD4+late). **RESULTS:** 844 HIV-positive patients were included in the analysis: 673 were HCV-negative and 171 were HCV-positive [92 (53.8%) subjects had HCV genotype 1; 58 (33.9%), genotype 3; 21 (12.3%), genotype 4]. Plasma HIV RNA (both baseline as highest value), nadir CD4+, being naïve, time to reach undetectable plasma HIV RNA, treatment with PI vs NNRTI were associated with an early immunological recovery; the occurrence of previous AIDS event, a history of injection drug use, and HCV infection were associated with failure to achieve an early immunological recovery. Variables associated with DeltaCD4+late immune recovery were baseline CD4+ value, plasma HIV RNA (both baseline as highest value), being naïve and time to reach undetectable plasma HIV RNA. HCV infection per se was not associated with a worse probability to reach late immunologic response, although among HCV infected patients, having a genotype 3 was associated with a worse immune recovery. At multivariable analysis, factors that remained associated with failure to achieve an early immunological response were being HCV infected and history of injection drug use, while those associated with a failure to achieve a late immunological response were being infected with HCV genotype 3 and older age. **CONCLUSIONS:** A blunted early immune recovery was observed in HCV infected patients, compared with HCV negative subjects, while late immune

recovery was not different among HCV infected as a whole and not infected subjects; only the subgroup of subjects infected with genotype 3 showed an impaired late immune recovery.

Is statin therapy safe in patients with HIV/hepatitis C coinfection? Stroup JS, Harris B. Proc (Bayl Univ Med Cent). 2010 Apr;23(2):111-3.

<http://www.ncbi.nlm.nih.gov/pubmed/20396416>

Statins are effective therapy for hypercholesterolemia and are commonly indicated in patients with HIV and hepatitis C virus infections. Unfortunately, in patients coinfecting with these viruses, the safety of statins has not been conclusively evaluated. We retrospectively evaluated five coinfecting patients in our outpatient clinic who received statin therapy. Although the sample size was small, we found that statins were safe in this population and recommend that further evaluation with a prospective controlled trial be undertaken to definitively answer this safety issue.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

A novel approach to evaluate traditional Chinese medicine treatment outcomes using pattern identification. Berle CA, Cobbin D, Smith N, Zaslowski C. J Altern Complement Med. 2010 Apr;16(4):357-67.

<http://www.ncbi.nlm.nih.gov/pubmed/20374102>

INTRODUCTION: Traditional Chinese Medicine (TCM), a modern interpretation of Chinese medicine, developed in the 1950s. It differentiates biomedical diseases into patterns. Each pattern comprises symptom/signs that have their own unique treatment protocol. Most TCM research has used fixed formula treatments for Western-defined diseases with outcomes often measured using objective biomedical markers. More recently, a number of trials have attempted to accommodate TCM clinical practice within the framework of rigorous evidence-based medical research. The aim of this article is to describe a novel outcome measure based on TCM patterns that was used in a pilot study for people with hepatitis C virus (HCV). **METHODS:** Sixteen (16) participants with HCV were enrolled in a randomized, controlled pilot study and allocated to a treatment or control group. TCM pattern diagnosis was obtained at baseline and used to guide acupuncture treatment for the treatment group. Each individual's primary, secondary, and tertiary TCM patterns were identified, which involved the systematic evaluation of the participant's information against the TCM patterns and conversion of the pattern to a percentage. Baseline and postintervention percentages for the three TCM patterns for the two groups were compared to assess change. **RESULTS:** There was a significant mean percentage decrease in pattern expression at week 12 compared to baseline for the secondary and tertiary patterns of the treatment group (56.3% versus 47.5%; $p = 0.045$ and 48.1% versus 33.6%; $p = 0.037$, respectively). No significant change was found for the primary, secondary, or tertiary patterns for the control group or for the primary pattern associated with the treatment group. **CONCLUSIONS:** The quantification of TCM patterns in this study permitted statistical evaluation of TCM pattern change. Previously, TCM pattern identification had only been used as a basis for developing the treatment protocol in clinical trials. This is the first time it has been employed as a novel outcome measure.

Aminofeel improves the sensitivity to taste in patients with HCV-infected liver disease.

Nagao Y, Matsuoka H, Kawaguchi T, Sata M. Med Sci Monit. 2010 Apr 1;16(4):PI7-12.

<http://www.ncbi.nlm.nih.gov/pubmed/20357731>

BACKGROUND: Patients with chronic liver diseases have a taste disorder and altered zinc metabolism. We investigated the effects of a supplement enriched with branched-chain amino acids (BCAA) (Aminofeel) on sensitivity to different tastes in patients with hepatitis C virus (HCV) infected liver disease. **MATERIAL/METHODS:** Nine patients (mean age 63.3+/-9.1 years) with HCV-related liver diseases were identified and examined for sensitivity to different tastes. Eight patients had no awareness of taste disorders, and 3 patients had oral lichen planus. We examined 4 tastes (sweet, salty, sour, and bitter) using a Taste Disk and sensitivity to different tastes was rated on a 6-point scale (I, II, III, IV, V, and VI). Each patient was given one sachet of Aminofeel after breakfast and another at bedtime for 90 days. **RESULTS:** Only one patient was aware of a taste disorder before administration of Aminofeel, but 4 patients had decreased gustatory sensitivity in the sour taste test, and 2 had it in the bitter taste test.

Sensitivity to sour tastes significantly increased after the administration of Aminofeel(R) (P=0.03). Sensitivity to sweet tastes increased after the administration of Aminofeel (P=0.06). Zinc value significantly increased after the administration of Aminofeel (P=0.02).

CONCLUSIONS: Patients with HCV-infected liver disease have decreased sensitivity to different tastes and decreased zinc levels. Some patients were unaware that they had a taste disorder. Aminofeel improved sensitivity to different tastes and increased zinc values. Thus, Aminofeel is a useful therapeutic agent for taste disorders.

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

Treatment of HBV/HCV coinfection. Potthoff A, Manns MP, Wedemeyer H. Expert Opin Pharmacother. 2010 Apr;11(6):919-28.

<http://www.ncbi.nlm.nih.gov/pubmed/20166841>

IMPORTANCE OF THE FIELD: Hepatitis B (HBV) and hepatitis C (HCV) virus infections are among the most common causes of advanced chronic liver disease worldwide. HBV/HCV coinfection is not uncommon with an estimated 7 - 20 million individuals affected worldwide. Patients with HBV/HCV coinfection have an increased risk for cirrhosis, hepatocellular carcinoma (HCC) and even death. **AREAS COVERED IN THIS REVIEW:** The pathophysiology of HBV/HCV coinfection is complex, as different patterns of virological dominance may occur, which can even fluctuate over time. Recently, combination of pegylated interferon (PEG-IFN) plus ribavirin has been explored in HBV/HCV coinfecting patients who are positive for HCV-RNA. HBV polymerase inhibitors may be indicated if HBV-DNA concentrations are above 2000 IU/ml. In this review, we summarize the epidemiology, viral interaction, its clinical features and the available treatment options. **WHAT THE READER WILL GAIN:** Insights into viral interaction of HBV/HCV coinfection and treatment individualization strategies are provided in the review. **TAKE HOME MESSAGE:** Detailed serological and virological evaluations are required for HBV/HCV coinfecting patients before initiation of antiviral therapy. At present, PEG-IFN-alpha plus ribavirin should be the treatment of choice in patients with dominant HCV replication. However, HBV rebound may occur after elimination of HCV, and thus close monitoring for both viruses is recommended even for patients with initially suppressed HBV-DNA.

Prevalence of hepatitis B and hepatitis C virus infections in France in 2004: social factors are important predictors after adjusting for known risk factors. Meffre C, Le Strat Y, Delarocque-Astagneau E, et al. *J Med Virol.* 2010 Apr;82(4):546-55.

<http://www.ncbi.nlm.nih.gov/pubmed/20166185>

To monitor the prevalence of hepatitis B and hepatitis C a cross-sectional survey was conducted in 2004 among French metropolitan residents. A complex sampling design was used to enroll 14,416 adult participants aged 18-80 years. Data collected included demographic and social characteristics and risk factors. Sera were tested for anti-HCV, HCV-RNA, anti-HBc and HBsAg. Data were analyzed with SUDAAN software to provide weighted estimates for the French metropolitan resident population. The overall anti-HCV prevalence was 0.84% (95% CI: 0.65-1.10). Among anti-HCV positive individuals, 57.4% (95% CI: 43.2-70.5) knew their status. Factors associated independently with positive anti-HCV were drug use (intravenous and nasal), blood transfusion before 1992, a history of tattoos, low socioeconomic status, being born in a country where anti-HCV prevalence >2.5%, and age >29 years. The overall anti-HBc prevalence was 7.3% (95%: 6.5-8.2). Independent risk factors for anti-HBc were intravenous drug use, being a man who has sex with men, low socioeconomic status, a stay in a psychiatric facility or facility for the mentally disabled, <12 years of education, being born in a country where HBsAg prevalence >2%, age >29 and male sex. The HCV RNA and HBsAg prevalence were 0.53% (95% CI: 0.40-0.70) and 0.65% (95% CI: 0.45-0.93), respectively. Among HBsAg positive individuals, 44.8% (95% CI: 22.8-69.1) knew their status. Anti-HCV prevalence was close to the 1990s estimates whereas HBsAg prevalence estimate was greater than expected. Screening of hepatitis B and C should be strengthened and should account for social vulnerability.

Analysis of hepatitis C virus strains circulating in Republic of the Congo. Cantaloube JF, Gallian P, Bokilo A, et al. *J Med Virol.* 2010 Apr;82(4):562-7.

<http://www.ncbi.nlm.nih.gov/pubmed/20166180>

The aim of this study was to assess the seroprevalence, viremia, genotype distribution, and demographic history of hepatitis C virus (HCV) in the Republic of the Congo. Testing was carried out on sera samples collected in 2005 from 807 Bantus belonging to the Kongo, Teke, and Ngala subgroups and 80 Pygmies. Positive HCV serology was found in 50 (5.6%) individuals including 31 (60%) who were viremic. Seroprevalence increased with age with a cutoff at 50 years: 2.8% <50 versus 12% >50. Twenty-one strains belonged to four described subtypes, that is, 4c in eight cases, 4h in two, 4k in three, and 4r in eight. Ten strains could not be assigned to any known subtype and may represent six new variants, that is, subtype 4 in five cases and subtype 2 in one. Evolutionary analysis of subtype 4c and 4r sequences indicated a period of enhanced transmission in the mid-twentieth century probably due to iatrogenic causes. This study underlines the high genetic diversity of strains in the Republic of the Congo with nine subtypes 4 and one subtype 2.

Hepatitis C virus infection in a Japanese leprosy sanatorium for the past 67 years.

Shiogama K, Teramoto H, Morita Y, et al. *J Med Virol.* 2010 Apr;82(4):556-61.

<http://www.ncbi.nlm.nih.gov/pubmed/20166169>

Oku-Komyo-En is one of the national leprosy sanatoria, located on a small island in Setouchi city, Okayama prefecture of Japan since 1938. Since autopsies were carried out routinely on almost all patients who had died in the sanatorium up to 1980, approximately 1,000 formalin-fixed autopsy tissue samples were available for analysis. When these samples were reviewed, the

pathological data indicated a sharp rise in the death rate caused by cirrhosis of the liver and hepatocellular carcinoma (HCC) since 1960 and 1970, respectively. Hepatitis C virus (HCV) infection is a common cause of HCC in Japan. The presence of HCV RNA was demonstrated in paraffin sections prepared from the autopsied liver tissue fixed in formalin for a prolonged period of time, by employing nested RT-PCR using type-specific primers. The data showed that HCV RNA was detectable in samples of the liver archived as early as 1940, representing the liver tissues kept in formalin for up to 67 years. HCV genotypes 1b and 2a were found by RT-PCR at 85.7% and 14.3%, respectively, in patients with leprosy

Performance evaluation of the Abbott RealTime HCV Genotype II for hepatitis C virus

genotyping. Sohn YH, Ko SY, Kim MH, Oh HB. Clin Chem Lab Med. 2010 Apr;48(4):469-74.

<http://www.ncbi.nlm.nih.gov/pubmed/20128734>

BACKGROUND: The Abbott RealTime hepatitis C virus (HCV) Genotype II (Abbott Molecular Inc.) for HCV genotyping, which uses real-time PCR technology, has recently been developed. **METHODS:** Accuracy and sensitivity of detection were assessed using the HCV RNA PHW202 performance panel (SeraCare Life Sciences). Consistency with restriction fragment mass polymorphism (RFMP) data, cross-reactivity with other viruses, and the ability to detect minor strains in mixtures of genotypes 1 and 2 were evaluated using clinical samples. **RESULTS:** All performance panel viruses were correctly genotyped at levels of >500 IU/mL. Results were 100% concordant with RFMP genotypic data (66/66). However, 5% (3/66) of the samples examined displayed probable genotypic cross reactivity. No cross reactivity with other viruses was evident. Minor strains in the mixtures were not effectively distinguished, even at quantities higher than the detection limit. **CONCLUSIONS:** The Abbott RealTime HCV Genotype II assay was very accurate and yielded results consistent with RFMP data. Although the assay has the advantages of automation and short turnaround time, we suggest that further improvements are necessary before it is used routinely in clinical practice. Efforts are needed to decrease cross reactivity among genotypes and to improve the ability to detect minor genotypes in mixed infections.

Identification of substance use and dependence among patients with viral hepatitis.

Jackson CB, Varon J, Ho A, et al. Dig Liver Dis. 2010 Apr 23. [Epub ahead of print]

Marks KM, Talal AH, Kreek MJ.

<http://www.ncbi.nlm.nih.gov/pubmed/20418192>

BACKGROUND: As drug abuse and addiction have been shown to decrease adherence to treatment of hepatitis C virus (HCV) or HIV, screening for substance use should be standard clinical practice in those undergoing an evaluation for these diseases. **AIMS:** To assess the effectiveness of the Kreek-McHugh-Schluger-Kellogg (KMSK) scale to quantify substance use and dependence among patients with viral hepatitis. **METHODS:** The KMSK scale, a validated instrument that quantifies lifetime use of alcohol, cocaine, heroin, and tobacco, was distributed to 161 consecutive patients referred to a hepatology clinic at an academic, tertiary-care center over a 1-year period. **RESULTS:** Of the 159 patients who returned the KMSK scale, 62% reported illicit drug use and 30% met defined criteria for lifetime dependence on cocaine or heroin. We found that 15% of our population at some time had been co-dependent on cocaine and heroin. The KMSK scale identified significantly more cocaine, heroin, and alcohol use than that detected through the medical record ($\chi^2=7.61$, $p<0.01$, $\chi^2=9.66$, $p<0.002$, respectively). Cocaine dependence was significantly higher among HCV/HIV co-infected than among mono-infected

patients ($\chi^2=5.46$, $p<0.02$). **CONCLUSIONS:** The KMSK scale may be useful to diagnose drug and alcohol use and dependence among patients undergoing evaluation for treatment of viral hepatitis.

Comorbidities associated with the increasing burden of hepatitis C infection. Basseri B, Yamini D, Chee G, Enayati PD, Tran T, Poordad F. *Liver Int.* 2010 Apr 8. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/20408945>

BACKGROUND: Hepatitis C virus (HCV) infection is implicated in an increasing number of liver transplantations, hospitalizations and healthcare costs. Aims: We present an updated assessment of comorbidities associated with HCV in comparison to the general US population. **METHODS:** Cross-sectional retrospective review of data from 800 patients with HCV evaluated between January 1998 and November 2007. Patient data were prospectively collected using a standardized questionnaire completed at the first encounter and was compared with general US epidemiological data. Odds ratios and 95% confidence intervals (CI) are reported. **RESULTS:** HCV conferred a 44% (CI 1.16-1.78) and 25% (CI 1.01-1.54) increased risk of diabetes (12.5 vs. 7.3-8.4%; $P=0.001$) and obesity (23.9 vs. 19.8-33.1%; $P=0.041$), respectively, compared with the US population. Human immunodeficiency virus (HIV) (5.3 vs. 0.3%; $P<0.001$) and end-stage renal disease (ESRD) (4.5 vs. 0.2%; $P<0.001$) were 16- and 13-fold more prevalent in HCV. Interestingly, HCV bestowed 90% decreased odds (CI 0.09-0.15) for hyperlipidaemia (12.3 vs. 53.2-56.1%; $P<0.001$). The HCV population had a higher prevalence of significant alcohol consumption (41.5 vs. 4.7%; $P<0.001$), current smoking (57.7 vs. 18.8-20.8%; $P<0.001$), drug use (46.8 vs. 14.6-15.6%; $P<0.001$), incarceration (6.6 vs. 2.7%; $P<0.001$) and tattoos (20.3 vs. 14%; $P=0.011$), as well as chronic fatigue (44.6 vs. 11.3-19%; $P<0.001$) and depression (29.3 vs. 5.0-10.3%; $P<0.001$). **CONCLUSION:** HCV poses an increasing healthcare burden associated with increased prevalence of diabetes, obesity, HIV, ESRD, maladaptive lifestyle habits and poor quality of life. Practitioners should be cognizant of these trends in order to appropriately manage these comorbidities.

Excellent superiority and specificity of COBAS TaqMan HCV assay in an early viral kinetic change during pegylated interferon alpha-2b plus ribavirin treatment. Ogawa E, Furusyo N, Toyoda K, et al. *BMC Gastroenterol.* 2010 Apr 16;10(1):38. [Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/20398383>

BACKGROUND: An early virological response (EVR) after the start of interferon (IFN) treatment for chronic hepatitis C leads to a successful virological outcome. To analyze an association between sustained virological response (SVR) and EVR by comparing TaqMan with Amplicor assays in HCV genotype 1-infected patients treated with pegylated (PEG)-IFN alpha-2b plus ribavirin (RBV). **METHODS:** We retrospectively analyzed a total of 80 HCV genotype 1 patients (39 SVR and 41 non-SVR patients), who received a complete 48-week treatment of PEG-IFN alpha-2b plus RBV. Serum HCV RNA levels were measured by both TaqMan and Amplicor assays for each patients at Weeks 2, 4, 8 and 12 after the start of the antiviral treatment. **RESULTS:** Of the 80 patients with undetectable HCV RNA by Amplicor, 17 (21.3%) patients were positive for HCV RNA by TaqMan. No significant difference in monitoring the HCV dynamics between TaqMan and Amplicor 10-fold method assays within the initial 12 weeks administration of the antiviral treatment was found. However, significant differences of the initial 12 week positive predictive rates for SVR were found between TaqMan (Weeks 4 and 8, 100% and 100%, respectively) and Amplicor (80.0% and 69.6%, respectively).

CONCLUSIONS: The COBAS TaqMan HCV assay is very useful for monitoring HCV viremia during antiviral treatment to predict a SVR in HCV genotype 1 patients.

Poor sleep quality predicts onset of either major depression or subsyndromal depression with irritability during interferon-alpha treatment.

Franzen PL, Buysse DJ, Rabinovitz M, Pollock BG, Lotrich FE. *Psychiatry Res.* 2010 May 15;177(1-2):240-245. Epub 2010 Apr 9.

<http://www.ncbi.nlm.nih.gov/pubmed/20381876>

Major depressive disorder (MDD) often occurs during pegylated IFN-alpha2 (IFN-alpha) treatment. Identifying who is at risk for MDD in this population is essential, and epidemiological studies suggest that sleep may be related to depression risk. Controlling for pre-existing depression symptoms, we therefore examined whether sleep quality prior to IFN-alpha treatment would predict subsequent MDD incidence during IFN-alpha treatment. Adults with hepatitis C but without current clinical MDD (n=86) were evaluated prior to IFN-alpha treatment and then prospectively monitored during treatment using self-report measures of sleep quality (PSQI), depression (BDI), and anger and irritability (AIAQ), as well as with Structured Clinical Interviews for DSM-IV Axis I Disorders (SCID-I). During IFN-alpha treatment, 19% developed MDD, 19% developed subsyndromal depression with irritability, and one developed mania. Controlling for baseline depression symptoms and past history of depression, patients with worse sleep quality (PSQI \geq 10) prior to treatment had a significantly shorter time until they developed MDD or any severe psychiatric problem. These findings may have important implications for understanding, predicting, and possibly preventing depression, particularly in individuals treated with IFN-alpha.

Serum apoptotic caspase activity in chronic hepatitis C and nonalcoholic Fatty liver disease.

Papatheodoridis GV, Hadziyannis E, Tsochatzis E, et al. *J Clin Gastroenterol.* 2010 Apr;44(4):e87-95.

<http://www.ncbi.nlm.nih.gov/pubmed/19881359>

BACKGROUND: Apoptotic caspases are substantially activated in liver and serum caspase activity has been suggested as a marker of early liver injury. **AIM:** To investigate whether serum levels of caspase-generated fragments of cytokeratin-18 are associated with the severity of histologic lesions in chronic hepatitis C virus (HCV) infection and nonalcoholic fatty liver disease (NAFLD). **METHODS:** We included 134 patients with chronic HCV infection and 58 patients with NAFLD, who consecutively underwent liver biopsy, and 40 healthy controls. Caspase-generated cytokeratin-18 fragment levels were blindly measured in stored serum samples. **RESULTS:** Median cytokeratin-18 fragment levels were lower in HCV-positive patients with minimal/mild than patients with moderate/severe histologic lesions (174 U/L vs. 223 U/L, $P<0.001$) offering moderate accuracy for differentiation between the 2 groups (c-statistic: 0.74). Cytokeratin-18 fragments levels were lower in healthy subjects (148 U/L) than patients with simple fatty liver (174 U/L, $P=0.013$) than patients with nonalcoholic steatohepatitis (355 U/L, $P<0.001$) offering excellent diagnostic accuracy for differentiation between the 2 latter groups (c-statistic: 0.87). **CONCLUSIONS:** Serum apoptotic caspase activity is associated with the severity of liver histologic lesions in both chronic HCV infection and NAFLD, but it has excellent diagnostic accuracy in NAFLD and moderate accuracy in chronic HCV patients.

Evaluation of a rapid, point-of-care test device for the diagnosis of hepatitis C infection.

Lee SR, Yearwood GD, Guillon GB, et al. Clin Virol. 2010 May;48(1):15-7. Epub 2010 Apr 1.
<http://www.ncbi.nlm.nih.gov/pubmed/20362493>

BACKGROUND: Despite considerable evolution in the quality of laboratory-based testing for detection of HCV, the availability of rapid, point-of-care tests may increase diagnoses by increasing opportunities for testing outside of traditional laboratory settings. **OBJECTIVES:** We evaluated the performance of a new, rapid HCV test that can be used with venous blood, finger stick blood, serum, plasma, or oral fluid and compared it to FDA-approved laboratory methods. **STUDY DESIGN:** HCV positive subjects as well as subjects at low risk for HCV were tested with the rapid test using all 5 specimen types and results compared to FDA-approved laboratory methods. In addition, performance was assessed in commercially available seroconversion panels. **RESULTS:** Sensitivity and specificity of the rapid test was equivalent to laboratory EIA and performance was comparable across all 5 specimen types. **CONCLUSIONS:** The OraQuick HCV Rapid Antibody Test appears suitable as an aid in the diagnosis of HCV infection.

Noninvasive markers of fibrosis and inflammation in clinical practice: prospective comparison with liver biopsy.

Anastasiou J, Alisa A, Virtue S, et al. Eur J Gastroenterol Hepatol. 2010 Apr;22(4):474-80.

<http://www.ncbi.nlm.nih.gov/pubmed/19887952>

BACKGROUND: The efficiency of transient elastography for the assessment of liver fibrosis has been evaluated mainly in patients with chronic hepatitis C and chronic hepatitis B, with few studies with nonviral chronic liver disease (CLD) such as autoimmune hepatitis, alcoholic liver disease and nonalcoholic steatohepatitis. In this study, we examined the value of transient elastography in a number of groups in comparison with the Fibrotest/Actitest (FT/AT), using the liver biopsy (LB) as the reference standard. **METHODS:** An unselected and consecutive group of 65 patients had an LB either as part of an initial diagnosis or of a follow-up assessment, and in addition had a transient elastography measurement [Fibroscan (FS)] and serum blood tests FT/AT performed before the LB. The group consisted of patients diagnosed with a variety of CLD: chronic hepatitis C (n=27), chronic hepatitis B (n=8), alcoholic liver disease (n=14), autoimmune hepatitis (n=13) and nonalcoholic steatohepatitis (n=4). **RESULTS:** FS optimal cutoff values were 9.70 kPa for F at least 2, 13.00 kPa for F at least 3, and 16.00 kPa for F=4. The areas under the receiver operating characteristic curve of FS and FT for F at least 2 were 0.88 versus 0.78 in the viral CLD group and 0.81 versus 0.70 in the nonviral CLD group and 0.87 versus 0.80 in all patients. The areas under the receiver operating characteristic curve for A at least 2 in all patients was 0.83. The optimal cutoff for A at least 2 was 0.50. **CONCLUSION:** FT/AT is a reliable method for predicting significant liver fibrosis and necroinflammation in both viral and nonviral CLD patients with a value measurement comparable with that of the FS.