



Caring Ambassadors Hepatitis C Program Newsletter

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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection.

McHutchison JG, Lawitz EJ, Shiffman ML, et al. N Engl J Med. 2009 Jul 22. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/19625712?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: Treatment guidelines recommend the use of peginterferon alfa-2b or peginterferon alfa-2a in combination with ribavirin for chronic hepatitis C virus (HCV) infection. However, these regimens have not been adequately compared. **METHODS:** At 118 sites, patients who had HCV genotype 1 infection and who had not previously been treated were randomly assigned to undergo 48 weeks of treatment with one of three regimens: peginterferon alfa-2b at a standard dose of 1.5 mug per kilogram of body weight per week or a low dose of 1.0 mug per kilogram per week, plus ribavirin at a dose of 800 to 1400 mg per day, or peginterferon alfa-2a at a dose of 180 mug per week plus ribavirin at a dose of 1000 to 1200 mg per day. We compared the rate of sustained virologic response and the safety and adverse-event profiles between the peginterferon alfa-2b regimens and between the standard-dose peginterferon alfa-2b regimen and the peginterferon alfa-2a regimen. **RESULTS:** Among 3070 patients, rates of sustained virologic response were similar among the regimens: 39.8% with standard-dose peginterferon alfa-2b, 38.0% with low-dose peginterferon alfa-2b, and 40.9% with peginterferon alfa-2a (P=0.20 for standard-dose vs. low-dose peginterferon alfa-2b; P=0.57 for standard-dose peginterferon alfa-2b vs. peginterferon alfa-2a). Estimated differences in response rates were 1.8% (95% confidence interval [CI], -2.3 to 6.0) between standard-dose and low-dose peginterferon alfa-2b and -1.1% (95% CI, -5.3 to 3.0) between standard-dose peginterferon alfa-2b and peginterferon alfa-2a. Relapse rates were 23.5% (95% CI, 19.9 to 27.2) for standard-dose peginterferon alfa-2b, 20.0% (95% CI, 16.4 to 23.6) for low-dose peginterferon alfa-2b, and 31.5% (95% CI, 27.9 to 35.2) for peginterferon alfa-2a. The safety profile was similar among the three groups; serious adverse events were observed in 8.6 to 11.7% of patients. Among the patients with undetectable HCV RNA levels at treatment weeks 4 and 12, a sustained virologic response was achieved in 86.2% and 78.7%, respectively.

CONCLUSIONS: In patients infected with HCV genotype 1, the rates of sustained virologic response and tolerability did not differ significantly between the two available peginterferon-ribavirin regimens or between the two doses of peginterferon alfa-2b.

Immunological and mutagenic actions of ribavirin monotherapy preceding combination therapy with interferon for patients with chronic hepatitis C. Ogawa K, Hige S, Nakanishi M, et al. Antivir Ther. 2009;14(4):513-22.

http://www.ncbi.nlm.nih.gov/pubmed/19578236?ordinalpos=5&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: We aimed to investigate the effects of ribavirin on hepatitis C virus (HCV). Immunological and virological effects were analysed in patients undergoing treatment with ribavirin monotherapy prior to the initiation of combination therapy with interferon-alpha. **METHODS:** A total of 25 patients with chronic HCV infection were enrolled in this study. All patients received ribavirin for 4 weeks during monotherapy; subsequently, interferon-alpha2b was additionally given as combined therapy. Patients were divided into two groups according to virological response. A rapid viral responder (RVR) was defined as a patient in whom HCV RNA became undetectable within 4 weeks after combination therapy. The changes of the T-helper (Th)1/Th2 subset of peripheral blood CD4(+) T-cells, serum cytokine levels and the alignment of the interferon sensitivity-determining region (ISDR) during ribavirin monotherapy were analysed by flow cytometry, ELISAs and sequencing methods. **RESULTS:** A total of 17 patients were classed as RVR. In the RVR group, the mean +/-sd serum alanine aminotransferase levels significantly decreased (before treatment 103 +/-92 IU/l and after treatment 57 +/-46 IU/l; P<0.05) during ribavirin monotherapy. The mean +/-sd Th1/Th2 ratio significantly increased (before treatment 13.9 +/-5.1 and after treatment 16.7 +/-6.2; P<0.05), but did not change in the non-RVR group. The levels of Th2 cytokines (interleukin-10 and soluble CD30) significantly decreased, especially in the RVR group. The mean +/-sd mutation rates of ISDR at the nucleotide level increased in the RVR group (before treatment 2.6 +/-0.9 sites/clone and after treatment 3.9 +/-1.6 sites/clone; P<0.05), but did not change in the non-RVR group. **CONCLUSIONS:** Ribavirin administration might increase the efficacy of interferon therapy for patients with chronic hepatitis C by stimulating the host immune system and promoting HCV gene mutation.

Losartan reduces the onset of type 2 diabetes in hypertensive Japanese patients with chronic hepatitis C. Arase Y, Suzuki F, Suzuki Y, et al. J Med Virol. 2009 Jul 21;81(9):1584-1590. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19623665?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The aim of this retrospective cohort study is to assess the cumulative development incidence and predictive factors for type 2 diabetes (T2DM) in HCV positive and hypertensive patients treated with losartan. Eighty Japanese patients were given 50 mg of losartan per day after diagnosis of hypertension (losartan group). Another 160 treated with spironolactone were selected as control (spironolactone group). Patients in spironolactone group were matched 1:2 with losartan group for age and sex. The mean observation period was 5.2 years in losartan group and 5.4 years in spironolactone group. An overnight (12 hr) fasting blood sample or a casual blood sample was taken for routine analyses during follow-up. The primary goal is the onset of T2DM. Evaluation was performed by using the Kaplan-Meier method and the cox proportional hazards analysis. Three patients in losartan group and 20 in spironolactone group developed T2DM. The 5th year cumulative appearance rates of T2DM were 5.4% in losartan group and 14.4% in spironolactone group. Multivariate cox proportional hazards analysis showed that T2DM development after the initiation of anti-hypertensive drugs occurred when anti-hypertensive drug was spironolactone (hazard ratio: 6.10; 95% confidence interval = 1.78-20.84; P = 0.004), histological staging was advanced (hazard ratio: 4.31; 95% confidence interval = 1.94-9.60; P < 0.001), fatty liver was present (hazard ratio: 3.28; 95% confidence interval = 1.47-7.27; P = 0.004), and patient had pre-diabetes (hazard ratio: 2.47; 95% confidence interval = 1.08-5.63; P = 0.032). Our results indicate losartan causes about 60% reduction of the onset of T2DM compared to patients treated with spironolactone.

Virological response at 4 weeks to predict outcome of hepatitis C treatment with pegylated interferon and ribavirin. Martinot-Peignoux M, Maylin S, Moucari R, et al. *Antivir Ther.* 2009;14(4):501-11.

http://www.ncbi.nlm.nih.gov/pubmed/19578235?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: Viral kinetics during therapy provides information on how to individualize treatment. To determine the benefit of assessing positive predictive values (PPVs) and negative predictive values (NPVs) of rapid virological responses (RVRs) and early virological responses (EVRs), on-treatment outcomes in chronic hepatitis C patients were examined. **METHODS:** A total of 408 patients (221 treatment-naïve) treated with pegylated interferon-alpha2b and ribavirin were included. Hepatitis C virus (HCV) RNA was measured at baseline, 4 weeks and 12 weeks. RVR was defined as undetectable HCV RNA at 4 weeks and EVR as $\geq 2 \log_{10}$ decrease in HCV RNA at 12 weeks. The additive value of RVR on predicting sustained virological response (SVR) was assessed with receiver operating characteristic (ROC) curves. **RESULTS:** SVR, RVR and EVR were observed in 46%, 23% and 78% of patients, respectively. PPVs of RVR were 96%, 100% and 100% in treatment-naïve patients, relapsers and non-responders, respectively. NPVs of failure to achieve EVR were 97%, 75% and 91%, in treatment-naïve patients, relapsers and non-responders, respectively. At 4 weeks, patients with RVR had the highest probability to achieve SVR (odds ratio 44.98 in the entire population and 32.95 in treatment-naïve patients). ROC curves showed the area under the ROC curve to be 0.758 versus 0.832 in the entire population and 0.795 versus 0.858 in treatment-naïve patients at baseline versus week 4, respectively. **CONCLUSIONS:** RVR is a strong predictor of SVR (PPV>96%) and failure to achieve EVR is a strong predictor of non-SVR (NPV>75%), independent of patients' pretreatment status. Added to baseline characteristics, RVR increased the accuracy to predict SVR. The combination of RVR and EVR provided complementary information, and thus provides a key opportunity to individualize treatment and improve the benefit/risk ratio of therapy.

Morphometric analysis of hepatic steatosis in chronic hepatitis C infection. Zubair A, Jamal S, Mubarak A. *Saudi J Gastroenterol.* 2009 Jan;15(1):11-4.

http://www.ncbi.nlm.nih.gov/pubmed/19568548?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND/AIMS: To quantitatively assess steatosis by a morphometric method and to study its relationship with other histological features of chronic hepatitis C (CHC). This was a comparative descriptive study. The study was carried out in the Department of Histopathology, Army Medical College, Rawalpindi, Pakistan, from March 2006 to March 2007. **METHODS:** Patients who had undergone a liver biopsy for the evaluation of hepatitis C virus (HCV) infection were included in the study. Demographic characteristics and laboratory data were collected at the time of biopsy. The first hundred biopsy specimens that met the inclusion criteria were assessed for grades of steatosis (semiquantitatively), diameter of fat globules (by a morphometric method), necroinflammation, and fibrosis (semiquantitatively). Liver biopsies were processed for paraffin embedding, stained with hematoxylin and eosin, whereas Gomori's Reticulin stain was used for the evaluation of fibrosis. **RESULTS:** Out of 46 cases showing fatty change, pansteatosis was observed in 24 (52%) patients: 12 (26%) cases had a pericentral and mid zonal distribution of fat globules and eight (17.5%) cases revealed a mid zonal pattern only. There were two (4.5%) cases in which fat globules were found in periportal and mid zonal areas. None of the histological parameters (the stage of fibrosis and grades of inflammation) had any significant correlation with these distribution patterns of steatosis. The diameter of fat droplets was quantified by morphometry. A mixed pattern of steatosis was observed more frequently (21 out of 46 cases): 17 cases had microglobules and eight

biopsies showed macroglobules. The size of the fat globules exhibited a significant correlation with the stage of fibrosis ($P < 0.0001$). The analysis of the grades of necroinflammation did not reveal any significant relationship with the diameter of fat globules. **CONCLUSIONS:** A mixed pattern of fat globules is more frequently observed in CHC, but macrovesicular steatosis is associated with a higher stage of fibrosis. Morphometry is recommended as one of the important tools for the follow-up of HCV-infected patients. Whether an accurate assessment of fat globule size by morphometry is preferred for the evaluation of patients before and after the antiviral therapy needs further research.

Predictive value of complete and partial early virological response on sustained virological response rates of genotype-4 chronic hepatitis C patients treated with PEG-interferon plus ribavirin. Elefsiniotis IS, Vezali E, Mihas K, Saroglou G. : Intervirology. 2009 Jul 14;52(5):247-251. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Elefsiniotis%20IS%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

OBJECTIVES: To investigate early viral kinetics, sustained virological response (SVR) rates and their predictors, in treatment-naïve, genotype-4-infected, chronic hepatitis C (CHC) patients treated with PEG-IFNalpha2b plus ribavirin. **PATIENTS AND METHODS:** In total, 58 patients were retrospectively analyzed. Early virological response (EVR) was defined as undetectable HCV-RNA (< 50 IU/ml) at week 12 (complete, cEVR) or at least a 2 log decrease in HCV-RNA levels (partial, pEVR). **RESULTS:** Thirty-one patients exhibited SVR (53.4%), 17 (29.3%) were non-responders and 10 (17.2%) relapsed. Thirty-seven patients (63.8%) exhibited EVR. The positive predictive values of EVR, cEVR and pEVR for the SVR achievement were 83.87, 54.83, and 29.03%, whereas their negative predictive values were 59.25, 77.77, and 81.48%, respectively. Both cEVR (OR 0.040, $p = 0.042$) and EVR (OR 0.016, $p = 0.006$) independently predicted SVR. Baseline viral load ($p < 0.001$), age ($p = 0.035$) and stage of liver disease ($p = 0.04$) were significantly related to the EVR achievement, whereas only baseline viral load ($p = 0.003$) and ethnicity ($p = 0.025$) predicted cEVR. **CONCLUSIONS:** Partial or complete EVR represent independent predictors of SVR in genotype-4-infected CHC patients, regardless of their baseline parameters. The absence of pEVR, rather than the absence of cEVR, should be used as an early indication for discontinuation of treatment in these patients.

Hepatic iron, serum ferritin, HFE mutation, and hepatic fibrosis in chronic hepatitis C.

Won JE, Jeong SH, Chung JI, Lee JH, Hwang SH, Kim JW, Lee SH, Kim N, Park YS, Lee DH, Kim H. Intervirology. 2009 Jul 14;52(5):239-246. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Won%20JE%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

OBJECTIVES: We studied the status of hepatic iron deposition and its relationship with blood iron indices, liver histology, and HFE gene mutations in Korean patients with chronic hepatitis C (CH-C). **METHODS:** 105 patients with CH-C who underwent pretreatment liver biopsy were consecutively enrolled. The hepatic iron deposition, histological activity and fibrosis were assessed by appropriate pathological scoring systems, clinical data including serum iron indices, and HFE gene mutation. **RESULTS:** Hepatic iron deposition was found in 37 patients (35%), which was not significantly associated with degree of hepatic fibrosis or steatosis. The serum ferritin level was elevated in 27% of the patients and was an independent factor associated with hepatic iron deposition by logistic regression; however, it was not significantly associated with hepatic fibrosis either. Only H63D heterozygote was found in 6 out of 48 patients (12.5%), which was not different from the prevalence of H63D mutation in the Korean population (8.5%). **CONCLUSIONS:** Hepatic iron deposition was uncommon and mild in Korean CH-C. Neither hepatic iron deposition

nor serum ferritin were significantly related to the severity of hepatic fibrosis, which does not support the significant role of iron in the progression of hepatic fibrosis.

Rapid loss of hepatitis C virus genotype 1b from serum in patients receiving a triple treatment with telaprevir (MP-424), pegylated interferon and ribavirin for 12 weeks. Suzuki F, Akuta N, Suzuki Y, et al. *Hepato Res.* 2009 Jul 10. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/19619256?ordinalpos=4&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

AIM: To evaluate the efficacy and safety of the triple treatment with telaprevir (MP-424), pegylated interferon (PEG-IFN) and ribavirin during 12 weeks on-treatment. **METHODS:** The triple treatment was given to 20 patients with chronic hepatitis C who had been infected with hepatitis C virus (HCV)-1b in high viral load (median: 6.8 log IU/mL [range: 5.5-7.2]), with a median age of 54 years (range: 36-65 years). They were followed for early dynamics of HCV RNA in serum during 12 weeks and side-effects. **RESULTS:** HCV RNA levels decreased by 4.8 logs by 7 days and 5.5 logs by 14 days. HCV RNA disappeared in 50% (10/20) at 2 weeks, 79% (15/19) at 4 weeks, 88% (14/16) at 6 weeks, 94% (15/16) at 8 weeks and 100% (13/13) at 12 weeks. HCV RNA disappeared equally frequently in 10 treatment-naive patients, six non-responders to IFN monotherapy and four non-responders to PEG-IFN and ribavirin. It was no different in the patients with and without amino acid substitutions reducing the response to IFN. The treatment was withdrawn in seven (35%) patients, mostly due to reduced hemoglobin of less than 8.5 g/dL, of whom six (86%) remained clear of HCV RNA at 12 weeks. **CONCLUSION:** HCV RNA was lost from serum rapidly and universally in patients infected with HCV-1b in high viral loads by the triple treatment. Because an early loss of HCV RNA correlates with high rates of sustained virological response (SVR), it would increase SVR substantially, and merit the patients who have not responded to previous therapies.

Symptomatic and pathophysiologic predictors of hepatitis C virus progression in pediatric patients. Henderson WA, Shankar R, Feld JJ, Hadigan CM. *Pediatr Infect Dis J.* 2009 Jul 10. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/19593250?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: The slow progression of hepatitis C virus (HCV) infection could ultimately negatively impact pediatric patients during their lifespan. This study describes the symptomatic and pathophysiologic presentation of HCV infection in a cohort of pediatric outpatients. **METHODS:** HCV-positive patients were identified by diagnosis codes from outpatient visits. Demographic and pathophysiologic indicators (comorbidities, reported symptoms, alanine transaminase, aspartate transaminase, gamma glutamyl transpeptidase, HCV viral load, genotype, and liver biopsy results) were collected and analyzed. **RESULTS:** We reviewed 62 patients with HCV infection who were from 3 months and 19 years of age (M +/- SD, 12.5 +/- 5.8 years). Sixty percent presented with clinical symptoms of fatigue, joint-abdominal pain, bruising/bleeding, or other non-specific symptoms. On liver biopsy (n = 35) 80% had evidence of inflammation, 57% had fibrosis, and 9% had steatosis. All patients with steatosis or cirrhosis reported symptoms. Males were significantly more likely than women to be symptomatic (58.3% vs. 41.7%, P = 0.04). Patients with symptoms were significantly older (M = 13.5 +/- 5.2 vs. 8.9 +/- 5.5 years, P = 0.003). There was a significant inverse relationship between viral load and symptoms (chi = 4.75, P = 0.03). Patients with low viral load (<2 million copies) were 5 times more likely to have symptoms than those with high viral loads (P = 0.03). Significance was also noted between HCV genotype and ALT levels (chi = 3.72, P = 0.05). There were no significant relationships between symptom status and race, comorbidities,

alanine transaminase, aspartate transaminase, gamma glutamyl transpeptidase, HCV genotype, or liver histology. **CONCLUSION:** Pediatric patients with HCV can have significant symptoms and physiologic liver changes related to HCV.

Sustained responders have better quality of life and productivity compared with treatment failures long after antiviral therapy for hepatitis C. John-Baptiste AA, Tomlinson G, Hsu PC, et al. *Am J Gastroenterol.* 2009 Jun 30. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22John-Baptiste%20AA%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

OBJECTIVES: We sought to compare the health status of patients with a sustained response to antiviral therapy for hepatitis C virus (HCV) infection with that of treatment failures, using health-related quality of life and preference (utility) measures. **METHODS:** Sustained responders had undetectable HCV viral levels 6 months after antiviral therapy. After antiviral therapy, participants completed, by mail or interview, the hepatitis-specific Medical Outcomes Study Short-Form 36-Item Health Survey (SF-36), the Health Utilities Index Mark 2/3 (HUI2/3), and time trade-off (TTO) for current health. The respondents provided information on demographics, history of substance abuse, comorbidities, and health history. Detailed clinical information was obtained by chart review. The respondents also indicated whether they missed work, volunteer opportunities, or household activities during the previous 3 months because of hepatitis C infection or its treatment. **RESULTS:** A total of 235 patients (133 responders and 102 treatment failures) completed questionnaires at an average of 3.7 years after the end of treatment. Treatment failures had significantly lower scores on the eight SF-36 domains ($P < 0.01$), lower scores on the hepatitis-specific domains ($P < 0.0001$), and lower physical (42.5 vs. 49.2) and mental (40.5 vs. 46.1) component summary scores ($P < 0.01$). HUI3 (0.57 vs. 0.70), HUI2 (0.74 vs. 0.80), SF-6D (0.65 vs. 0.71), and TTO (0.84 vs. 0.89) were lower for treatment failures ($P < 0.05$). The regression-adjusted difference in HUI3, SF-6D, physical summary score, and mental summary score was 0.08 ($P = 0.04$), 0.05 ($P = 0.004$), 5.22 ($P = 0.001$), and 5.73 ($P < 0.0001$), respectively. Differences in the HUI2 and TTO scores were not significant after adjustment for demographic and clinical variables. Treatment failures were more likely to have missed work, volunteer opportunities, or household activities in the previous 3 months because of hepatitis C infection or its treatment (44 vs. 9%, $P < 0.001$). **CONCLUSIONS:** Patients with a sustained response to antiviral therapy for chronic HCV infection have better quality of life than treatment failures do. Our study validates the benefits associated with the sustained response to antiviral therapy in a real-world clinic population and shows that these benefits are maintained over the long term.

Pegylated interferon and ribavirin-induced depression in chronic hepatitis C: role of personality. Castellvi P, Navinés R, Gutierrez F, et al. *J Clin Psychiatry.* 2009 Jun;70(6):817-28.
http://www.ncbi.nlm.nih.gov/pubmed/19573480?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

OBJECTIVE: Pegylated interferon (PegIFN) and ribavirin (RBV) treatment for the hepatitis C virus (HCV) infection can induce depressive episodes. Personality traits have been associated with mood disorders. The aim of this study was to evaluate the personality profile as a risk factor for induced depression by PegIFN and RBV treatment in patients with HCV. **METHOD:** In a prospective cohort study, 204 consecutive HCV outpatients who received PegIFN and RBV were assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders and the Temperament and Character Inventory-Revised (TCI-R). Moreover, the Patient Health Questionnaire and the Hospital Anxiety and Depression Scale were administered at baseline and at 4, 12, 24, and/or 48

weeks of treatment. Patients were recruited between September 2003 and December 2006.

RESULTS: One hundred eighteen patients (57.8%) were men. The mean (SD) age was 44.39 (10.4) years. The incidence of induced depression during the 48 weeks of antiviral treatment was 73 (42%). Low self-directedness dimension (HR = 0.63, 95% CI = 0.446 to 0.890, $p = .009$), baseline subclinical depression levels (HR = 1.113, 95% CI = 1.023 to 1.22, $p = .013$), and history of mood disorders (HR = 0.372, 95% CI = 0.220 to 0.629, $p < .001$) were independent predictive factors for induced depression during PegIFN and RBV treatment. Other predictive personality TCI-R subscales were enlightened second nature (HR = 2.939, 95% CI = 1.423 to 6.071, $p = .004$), fatigability (HR = 0.421, 95% CI = 0.237 to 0.749, $p = .01$), and disorderliness (HR = 0.449, 95% CI = 0.248 to 0.815, $p = .008$). **CONCLUSION:** Low self-directedness, depressive symptoms at baseline, and history of previous mood disorders may predict induced depression by PegIFN and RBV in euthymic HCV patients.

Serum HCV RNA levels and HCV genotype do not affect insulin resistance in non-diabetic patients with chronic hepatitis C: a multicentre study. Tsochatzis E, Manolakopoulos S, Papatheodoridis GV, et al. *Aliment Pharmacol Ther.* 2009 Jul 9. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Tsochatzis%20E%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND/AIM: Chronic hepatitis C (CHC) induces insulin resistance (IR) and subsequently diabetes. We examined viral, metabolic and histological predictors of IR in 275 CHC patients to test the hypothesis that IR differs among HCV genotypes and that viral replication directly affects IR. **METHODS:** We studied 275 non-diabetic treatment-naïve CHC patients. Histological lesions were evaluated according to Ishak. IR was assessed using HOMA-IR.

RESULTS: HOMA >3.0 was found in 37% of patients and was independently associated with higher BMI and GGT. In genotype non-3 patients, HOMA >3.0 was associated with higher BMI and GGT values, while no significant association was noted in genotype 3 patients. In non-obese patients with minimal fibrosis, HOMA >3.0 was found in 20% of cases without significant differences among genotypes. No association between HOMA >3.0 and HCV-RNA levels was found. Severe fibrosis (stage 5-6) was significantly associated with older age (OR:1.048), HOMA-IR (OR:1.177), necroinflammation (OR:2.990) and higher ALT (OR:1.009) and GGT (OR:1.006).

CONCLUSIONS: IR develops at early stages of CHC without significant differences among genotypes. It is more frequent in obese patients with steatosis and contributes to fibrosis progression. However, IR does not seem to be associated with viremia and therefore its exact pathogenetic mechanism in CHC remains elusive.

Correlates and prognostic value of the first-phase hepatitis C virus RNA kinetics during treatment. Durante-Mangoni E, Zampino R, Portella G, Adinolfi LE, Utili R, Ruggiero G. *Clin Infect Dis.* 2009 Aug 15;49(4):498-506.

http://www.ncbi.nlm.nih.gov/pubmed/19591593?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: Analysis of hepatitis C virus (HCV) RNA kinetics during antiviral therapy may allow estimation of the probability of response. **METHODS:** To assess clinical and virological correlates and the predictive value of first-phase HCV RNA kinetics during pegylated interferon and ribavirin treatment, we studied 119 patients with chronic hepatitis C who were treated with pegylated interferon and ribavirin. HCV RNA level was measured 5 min before and 2, 14, and 28 days after the start of treatment. For each patient the Delta(t0-t2) log₁₀ HCV RNA value was calculated, which indicates the relative reduction in HCV RNA level from before treatment to day 2 after logarithmic transformation. **RESULTS:** A Delta(t0-t2) log₁₀ HCV RNA value $< \text{or} = 0.8$

showed a 95% negative predictive value for virological response, whereas one >2.5 had a 93% positive predictive value for virological response, independent of genotype and histology. The Delta(t0-t2) log(10) HCV RNA value was strictly related to final treatment outcome and could differentiate not only patients with a sustained virological response from nonresponders but also patients who experienced relapse from the former. The Delta(t0-t2) log(10) HCV RNA value was highest among patients infected with genotypes 2 and 3 and was lowest among patients infected with genotype 1. It decreased with increasing grades of fibrosis and steatosis and was also inversely related to gamma-glutamyl transpeptidase (GGT) level and HOMA-IR (homeostasis model assessment for insulin resistance) score. In multivariate analysis, [Formula: see text] log(10) HCV RNA value was the strongest predictor of sustained virological response and appeared to be independently related to viral genotype and GGT level. **CONCLUSION:** HCV RNA kinetics has strong predictive value. It correlates with virological and clinical parameters that are known predictors of antiviral treatment outcome, including insulin resistance. The measurement of HCV load as early as 2 days after the start of pegylated interferon and ribavirin is a useful tool for the prediction of treatment outcome in individual patients and should be used in clinical practice.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

The role of nucleoside transporters in the erythrocyte disposition and oral absorption of ribavirin in the wild-type and equilibrative nucleoside transporter 1 (-/-) mice. Endres CJ, Moss AM, Govindarajan R, Choi DS, Unadkat JD. J Pharmacol Exp Ther. 2009 Jul 14. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19602549?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Ribavirin is the treatment of choice for hepatitis C virus infection. Ribavirin is a substrate of several nucleoside transporters, including the equilibrative nucleoside transporter 1 (Ent1) and the concentrative nucleoside transporter 2. To determine the role of Ent1 in ribavirin absorption and erythrocyte distribution, we examined its pharmacokinetics in Ent1-null mice. After intravenous administration, we found that the erythrocyte AUC_{0-12hr} was reduced 3.05-fold along with 2.63-fold reduction of erythrocyte versus plasma AUC-ratio in the Ent1(-/-) mice, whereas there was no significant difference in the plasma AUC_{0-12hr} between Ent1(+/+) and Ent1(-/-) mice. After 48 hours, we found a similar fraction of ribavirin or total radioactivity excreted in the urine between the Ent1(+/+) and Ent1(-/-) mice. After oral administration of three different doses, 0.024, 0.24 and 6.1 mg/kg, we found that the dose-normalized plasma AUC_{0-12hr} of ribavirin was 69.7±12.0, 20.7±1.5 and 18.3±2.7 min/L respectively in the Ent1(+/+) mice and 18.9±2.8, 13.0±0.5 and 12.2±1.0 min/L respectively in the Ent1(-/-) mice. Interestingly, at the highest dose, the dose-normalized plasma AUC_{0-30min}, AUC_{0-12hr} and C_{max} in the Ent1(+/+) mice were decreased 4.0, 3.8 and 3.4-fold respectively compared with the lowest dose, suggesting absorption was saturated at the highest dose we used. The dose-normalized plasma AUC_{0-12hr} was 3.7 and 1.5-fold lower at the lowest and the highest dose respectively in the Ent1(-/-) mice compared to those of the Ent1(+/+) mice. Our findings indicate that Ent1 plays a significant role in the oral absorption and erythrocyte distribution of ribavirin.

Non-structural 5A protein of hepatitis C virus induces a range of liver pathology in transgenic mice. Wang AG, Lee DS, Moon HB, et al. J Pathol. 2009 Jun 18. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/19621337?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Hepatitis C virus (HCV) is a major cause of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC). However, the mechanism of HCV pathogenesis is not well understood. Our previous in vitro studies suggested that non-structural 5A (NS5A) protein may play an important role in liver pathogenesis. To elucidate the mechanism of HCV-induced liver pathogenesis, we investigated the histopathological changes of liver in transgenic mice harbouring the NS5A gene. We generated transgenic mice harbouring HCV NS5A gene under the control of hepatitis B virus (HBV) enhancer. Pathological changes were analysed by immunohistochemical staining and western blot analysis. Lipid composition and reactive oxygen species (ROS) production in NS5A transgenic mice were analysed. HCV NS5A transgenic mice developed extraordinary steatosis over 6 months old and induced HCC in some mice. NS5A was co-localized with apolipoprotein A-I in fatty hepatocytes. In addition, the extraordinarily high levels of ROS, NF-kappaB and STAT3 were detected in hepatocytes of NS5A transgenic mice. These data suggest that NS5A, independent of other HCV viral proteins, may play an important role in the development of hepatic pathologies, including steatosis and hepatocellular carcinoma in transgenic mice.

Predictive value of suppressor of cytokine signal 3 (SOCS3) in the outcome of interferon therapy in chronic hepatitis C. Miyaaki H, Ichikawa T, Nakao K, et al. Hepatol Res. 2009 Jul 13. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19624774?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

AIMS: Suppressor of cytokine signaling 3 (SOCS3) can suppress Janus kinase (JAK)-signal transducers and activators of transcription (STAT) signaling by blocking an IFN-induced protein. In this study, the relationship between SOCS3 and phosphorylation of STAT1 in the liver and outcome of interferon therapy were examined. **METHODS:** Prior to interferon treatment, we immunostained for SOCS3 and phosphorylated-STAT1 (P-STAT1) in 59 liver specimens from chronic hepatitis C virus (CHC) patients and compared the expression of SOCS3 and clinicopathological factors. Fifty-one patients were receiving peg-interferon alpha-2b and ribavirin therapy and also compared interferon therapy effect and the expression of SOCS3. **RESULTS:** Immunostaining for SOCS3 was mainly seen in the periportal area. The concentration of P-STAT1 nuclei was significantly larger in specimens with < 30% area immunostaining to SOCS3 than those in which this area was >= 30% (10.6 +/- 8.8 vs. 4.6 +/- 6.1, P = 0.004). SOCS3 immunostaining score was significantly correlated with aspartate amino transferase (r = 0.373, P = 0.003), alanine amino transferase (r = 0.337, P = 0.008), platelets (r = -0.273, P = 0.037), and homeostatic model assessment (r = 0.339, P = 0.008). On univariate analysis and multivariate analysis, SOCS3 immunostaining score (0 or 1) and age (<60 years old) were significant predictors of interferon response (odds ratio 10.888; P = 0.010; odds ratio 3.817, P = 0.045 respectively). **CONCLUSION:** SOCS3 expression in the liver prior to interferon therapy was correlated with increased insulin resistance and might be a useful predictor of HCV clearance by interferon therapy.

FOXP3+ expression in hepatitis C virus specific CD4+ T cells during acute hepatitis C.

Heeg MH, Ulsenheimer A, Grüner NH, et al. Gastroenterology. 2009 Jul 10. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Heeg%20MH%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND & AIMS: Down regulation of hepatitis C virus specific CD4(+) T cell responses is a hallmark of chronic viral persistence in acute hepatitis C. FOXP3(+) CD25(+) CD4(+) regulatory T cells can modulate hepatitis C virus specific immune responses in vitro but the role of virus specific regulatory T cells in the pathogenesis of chronic viral persistence is unknown. **METHODS:** Two novel HLA-DR15 tetramers were synthesized to study the kinetics and phenotype of FOXP3(+) expressing hepatitis C virus specific CD4(+) T cells from ten patients with acute hepatitis C and 15 patients with chronic hepatitis C. **RESULTS:** In acute hepatitis C, generally only a low percentage of hepatitis C virus specific CD4(+) T cells expressed FOXP3(+) (mean 2.5 % in self-limited acute hepatitis C vs. 2.4% in patients with evolving chronic hepatitis C). Although distinct but short-lived increases in virus specific FOXP3(+)CD4(+) T cells occurred in three patients (30%, 26%, and 7% of tet(+) CD4(+) T cells, respectively) these did not correlate with the evolution of chronic hepatitis C. Hepatitis C virus specific FOXP3+CD4+ T cells displayed a distinct phenotype with only 10% expressing CD25 and 40% being CD127low. Interestingly, this phenotype of FOXP3+CD4+ T cells was already expanded in bulk CD4+ T cells in patients with chronic hepatitis C. **CONCLUSIONS:** Although short-lived increases in HCV specific FOXP3(+)CD4(+) T cells occur during the course of acute hepatitis C we could not demonstrate an association of hepatitis C virus specific regulatory T cells and persistent viremia.

Specific activation of 2'-5'oligoadenylate synthetase gene promoter by hepatitis C virus-core protein: a potential for developing hepatitis C virus targeting gene therapy. Wang Y, Mao SS, He QQ, Zi Y, Wen JF, Feng DY.

http://www.ncbi.nlm.nih.gov/pubmed/19575500?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

AIM: To examine whether 2'-5'oligoadenylate synthetase (OAS) gene promoter can be specifically activated by hepatitis C virus (HCV)-core protein. **METHODS:** Human embryo hepatic cell line L02 was transfected with pcDNA3.1-core plasmid and selected by G418. Expression of HCV-core was detected by reverse transcription polymerase chain reaction and Western blotting. The OAS promoter sequence was amplified from the genomic DNA and inserted into pGL3-basic vector. The resultant pGL3-OAS-Luci plasmid was transiently transfected into L02/core cells and luciferase activity was assayed. **RESULTS:** L02/core cell line stably expressing HCV-core protein was established. The pGL3-OAS-Luci construct exhibited significant transcriptional activity in the L02/core cells but not in the L02 cells. **CONCLUSION:** HCV-core protein activates the OAS gene promoter specifically and effectively. Utilization of OAS gene promoter would be an ideal strategy for developing HCV-specific gene therapy.

HIV/HCV COINFECTION

Analysis of the efficacy of treatment with peginterferon alpha-2a and ribavirin in patients coinfecting with hepatitis B virus and hepatitis C virus. Yu JW, Sun LJ, Zhao YH, Kang P, Gao J, Li SC. Liver Int. 2009 Jul 7. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Yu%20JW%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

ABSTRACT OBJECTIVE: To study the virological features of patients coinfecting with hepatitis B virus (HBV) and hepatitis C virus (HCV) and the efficacy of combination therapy with peginterferon alpha-2a and ribavirin in these patients. **METHODS:** The epidemiological and virological data of 50 patients coinfecting with HBV and HCV were analysed. The virological response rates of patients treated with peginterferon alpha-2a and ribavirin between the HBV and

HCV coinfection group and the HCV mono-infection group were compared. **RESULTS:** HCV-dominant virus strains accounted for 92.0% of the 50 coinfecting individuals, and HCV- and HBV-dominant virus strains accounted for the remaining 8.0%. The HBV DNA level of the patients coinfecting with HBV and HCV was $4.6 \pm 0.9 \log_{10}$ copies/ml, which was significantly lower than that in the HBV mono-infection group ($5.9 \pm 1.2 \log_{10}$ copies/ml) ($t=5.964$, $P<0.01$). The HBeAg-positive rate (12.0%, 6/50) of the coinfection group was significantly lower than (45.3%, 19/42) that of the HBV mono-infection group ($\chi^2=12.743$, $P<0.01$). The partial early virological response (pEVR) rate and the end-of-treatment virological response (ETVR) rate (50.0%, 15/30; 90.0%, 27/30) of patients with genotype 1 in the coinfection group were significantly higher than those (16.0%, 4/25; 56.0%, 14/25) in the HCV mono-infection group ($\chi^2=6.971$, $P=0.008$; $\chi^2=8.307$, $P=0.004$). The relapse rate (55.6%, 15/27) of patients with genotype 1 in the coinfection group was significantly higher than that (21.4%, 3/14) in the HCV mono-infection group ($\chi^2=4.360$, $P=0.037$). The sustained virological response (SVR) rate (40.0%, 12/30) of patients with genotype 1 in the coinfection group was compared with that of the HCV mono-infection group (44.0%, 11/25) ($\chi^2=0.090$, $P=0.765$). There was no significant difference in the on-treatment virological response, ETVR, SVR and relapse rates between two groups for patients with genotype 2. The incidence of side effects (30%, 15/50) of patients in the coinfection group was significantly higher than that (13%, 6/46) in the HCV mono-infection group ($\chi^2=4.031$, $P=0.045$). The reactivation rate of HBV DNA (33.3%, 9/27) with HCV SVR was significantly higher than that of patients without SVR (8.7%, 2/23) ($\chi^2=4.393$, $P=0.036$). **CONCLUSIONS:** The replication of HBV was suppressed, and HCV was the dominant virus strain. Compared with HCV-mono-infected patients, pEVR, ETVR and relapse rates of patients with genotype 1 in the coinfection group were high, while they shared similar SVR rates. HBV and HCV coinfection had no impact on the rate of virological response for genotype 2.

Hepatitis B virus and hepatitis C virus interaction in Huh-7 cells. Eyre NS, Phillips RJ, Bowden S, Yip E, Dewar B, Locarnini SA, Beard MR. *J Hepatol.* 2009 Jun 3. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/19596477?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND/AIMS: Co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) increases the risk of development and the severity of chronic liver disease. Although dominant and suppressive effects of each virus over the other have been reported in vivo, in vitro studies of HBV/HCV co-infection have been limited to analysis of the effects of over-expression of HCV proteins on HBV replication. **METHODS:** We have re-examined HBV/HCV interactions in Huh-7 cells following co-infection with cell culture-propagated HCV (HCVcc; genotype 2a) and a recombinant adenovirus vector capable of delivering a replication-competent HBV genome (AdHBV; genotype A). **RESULTS:** While intracellular HCV RNA levels were significantly increased when cells were pre-infected with AdHBV, HCV replication and virion secretion were not altered by simultaneous infection with AdHBV or AdHBV superinfection of HCV-infected cells. Likewise intracellular and secreted HBV DNA levels and HBV promoter activities were either unchanged or modestly increased by HCVcc infection. Despite this, HCV E2 and HBsAg proteins colocalized extensively in co-infected cells suggesting shared stages in viral egress. **CONCLUSIONS:** These studies indicate that there is little direct interaction of HBV and HCV in co-infected hepatocytes and imply that indirect effects of host-viral interactions dictate viral dominance in HBV/HCV co-infected individuals.

Prevalence of cryoglobulinaemia in hepatitis C virus- and hepatitis C virus/human immunodeficiency virus-infected individuals: implications for renal function. Lapinski TW, Parfieniuk A, Rogalska-Plonska M, Czajkowska J, Flisiak R. *Liver Int.* 2009 Jul 7. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Lapinski%20TW%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND AND AIMS: Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) demonstrate an affinity towards lymphocytes B, stimulating the production of cryoglobulins. Deposits of cryoprecipitates contribute to glomerulonephritis and renal failure. The presence of cryoglobulins was investigated in the sera of HCV-monoinfected and HCV/HIV-coinfected individuals. Associations between types of cryoglobulins and HCV genotypes, viral load and renal function tests were also evaluated. **PATIENTS AND METHODS:** Seventy-seven patients were enrolled in this study. Forty-four were HCV infected and 33 were HCV/HIV coinfecting.

Cryoglobulins were detected in the sera by electrophoresis and immunofixation. Serum urea and creatinine concentration, glomerular filtration rate (GFR) and serum cystatin C concentration (CC) were analysed to evaluate renal function. The control group included 16 healthy individuals.

RESULTS: The occurrence of cryoglobulinaemia in HCV-monoinfected patients was 55%, whereas in HCV/HIV-coinfected patients it was 64%. Mixed cryoglobulinaemia type II was determined in 34%, whereas type III in 25%. The prevalence of cryoglobulinaemia was significantly higher in infection with HCV genotype 1 vs. genotype 3 (65 vs. 50%; $P < 0.01$). The most frequently occurring heavy chains were gamma-type (96%). Light chains, the kappa-type, were detected in all patients. The CC concentration was significantly higher in HCV/HIV-coinfected patients compared with controls (718 vs. 392 ng/ml; $P < 0.005$) or HCV-monoinfected patients (508 ng/ml; $P < 0.007$). There was correlation between the serum CC concentration and the incidence of cryoglobulinaemia ($R = 0.44$; $P < 0.00015$), which was particularly evident in HCV monoinfection ($R = 0.43$; $P < 0.0034$).

CONCLUSIONS: Genotype-1 infection is an important risk factor for cryoglobulinaemia. Standard renal function tests are not sufficient for the prediction of renal failure in HCV-infected patients. Serum CC concentration allows to establish an early diagnosis of renal insufficiency related to cryoglobulinaemia.

Sustained virological response to interferon plus ribavirin reduces liver-related complications and mortality in patients coinfecting with human immunodeficiency virus and hepatitis C virus. Berenguer J, Alvarez-Pellicer J, Martín PM, et al. *Hepatology.* 2009 Jul 2. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19575364?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Human immunodeficiency virus (HIV) infection modifies the natural history of chronic hepatitis C, thus promoting more rapid progression to cirrhosis and end-stage liver disease. **The objective** of our study was to determine whether hepatitis C virus (HCV) clearance is associated with improved clinical outcomes in patients positive for HIV and HCV. It was an ambispective cohort study carried out in 11 HIV units in Spain and involved 711 consecutive patients positive for HIV/HCV who started interferon plus ribavirin therapy between 2000 and 2005. We measured sustained virologic response (SVR), i.e., undetectable HCV RNA at 24 weeks after the end of treatment, and clinical outcomes, defined as death (liver-related or non-liver-related), liver decompensation, hepatocellular carcinoma, and liver transplantation. Of 711 patients who were positive for HIV/HCV, 31% had SVR. During a mean follow-up of 20.8 months (interquartile range: 12.2-38.7), the incidence rates per 100 person-years of overall mortality, liver-related mortality, and liver decompensation were 0.46, 0.23, and 0.23 among patients with SVR and 3.12, 1.65, and 4.33 among those without SVR (P

= 0.003, 0.028, and <0.001 by the log-rank test), respectively. Cox regression analysis adjusted for fibrosis, HCV genotype, HCV RNA viral load, Centers for Disease Control and Prevention clinical category, and nadir CD4+ cell count showed that the adjusted hazard ratio of liver-related events was 8.92 (95% confidence interval, 1.20; 66.11, P = 0.032) for nonresponders in comparison with responders and 4.96 (95% confidence interval, 2.27; 10.85, P < 0.001) for patients with fibrosis grade of F3-F4 versus those with F0-F2. Because this was not a prospective study, selection and survival biases may influence estimates of effect. **CONCLUSION:** Our results suggest that the achievement of an SVR after interferon-ribavirin therapy in patients coinfecting with HIV/HCV reduces liver-related complications and mortality.

Predictability of sustained virological response to pegylated interferon alpha-2b Plus ribavirin therapy by week-8 viral response in HIV-positive patients with chronic hepatitis C virus infection. Angeli E, Mainini A, Cargnel A, et al. *Curr HIV Res.* 2009 Jul;7(4):447-55.

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Angeli%20E%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

Chronic hepatitis C is frequent and aggressive in HIV-positive patients. Identification of early predictors of response to anti-HCV therapy is needed for a lower rate of response and higher discontinuations, compared to HCV mono-infected subjects. The aim of our study was to evaluate the predictive value of virological response (VR) at week 4-8-12 of Pegylated interferon alpha-2b (PEG-IFN) plus ribavirin (RBV) on sustained virological response (SVR) in HIV-HCV co-infected patients. 100 patients were treated with PEG-IFN (1.5 mcg/Kg/w) plus RBV (> or =10.6 mg/kg/d) and randomized for 24-48 or 48-72 weeks, respectively for genotype 2-3 and 1-4, in case of response (HCV-RNA PCR negativity) at the end of standard therapy (24 weeks for genotype 2-3, 48 weeks for genotype 1-4). Transcription-Mediated Amplification (TMA) assay for HCV-RNA was also applied. 27 patients reached end-of-treatment response (9 genotype 1-4, 18 genotype 2-3), 21 achieved SVR (8 genotype 1-4, 13 genotype 2-3). 35 patients dropped, 15 due to side-effects. SVR was statistically related to lower baseline HCV-RNA and to VR at week 4-8-12, with PPV 64%, 53% and 58%, and NPV 81%, 96% and 88%, respectively. In 27 patients, TMA was performed and confirmed standard PCR, except in two cases of relapse, who were PCR negative but TMA positive at week-12. In conclusion, VR at week 8 showed the highest NPV on SVR (96%). The study of viral kinetics requires further investigations in HIV-positive patients to guarantee a cost-effective therapy and to guide individually the duration of treatment. In this setting, TMA might be useful.

Risk of developing specific AIDS-defining illnesses in patients coinfecting with HIV and hepatitis C virus with or without liver cirrhosis. d'Arminio Monforte A, Cozzi-Lepri A, Castagna A, et al. *Clin Infect Dis.* 2009 Aug 15;49(4):612-22.

http://www.ncbi.nlm.nih.gov/pubmed/19591597?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: There are few data concerning the risk of specific opportunistic diseases in patients with and without hepatitis C virus (HCV) infection. We evaluated the correlation between the occurrence of different AIDS-defining illnesses (ADIs) and chronic HCV infection or HCV-related liver cirrhosis in a large Italian cohort of human immunodeficiency virus (HIV)-infected subjects. **METHODS:** Subjects were stratified into 2 groups: patients without HCV coinfection and with persistently normal aminotransferase levels and patients with HCV coinfection. The patients with HCV coinfection were stratified according to the diagnosis of liver cirrhosis. The incidences of new ADIs were calculated as the number of events per 1000 person-years of follow-up. The rates in the 2 groups were compared using a Poisson regression model adjusted for potential confounders. **RESULTS:** We observed a total of 496 ADIs among 5397 patients with 25,105 person-years of

follow-up (50% tested positive for HCV). HCV coinfection was associated with increased risk of developing an ADI (adjusted relative rate [ARR], 2.61; 95% confidence interval [CI], 1.88-3.61), specifically bacterial infection (ARR, 3.15; 95% CI, 1.76-5.67), HIV-related disease (ARR, 2.68; 95% CI, 1.03-6.97), and mycotic disease (ARR, 3.87; 95% CI, 2.28-6.59) but not non-Hodgkin lymphoma (ARR, 0.88; 95% CI, 0.22-3.48). The rate of mycotic infection, bacterial infection, toxoplasmosis, and HIV-related ADI among patients with cirrhosis were significantly higher than that among HIV-monoinfected patients, and the risk was greater than that estimated for HCV antibody-positive patients without cirrhosis. **CONCLUSIONS:** HIV-related bacterial and mycotic infections are strongly associated with positive HCV serostatus and HCV-related cirrhosis. Clinicians should take into account these data when making decisions on initiation of antiretroviral therapy for HCV-coinfected individuals.

Sustained virological response after early antiviral treatment of acute hepatitis C virus and HIV coinfection. Schulze Zur Wiesch J, Pieper D, Stahmer I, et al. Clin Infect Dis. 2009 Aug 1;49(3):466-72.

http://www.ncbi.nlm.nih.gov/pubmed/19580412?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: Limited data exist describing the clinical outcome and immunological response primed during simultaneously acquired acute hepatitis C virus (HCV) and human immunodeficiency virus (HIV) coinfection. We present detailed clinical and immunological analysis of 3 individuals after concomitant infection with acute HCV and primary HIV. **METHODS:** In addition to longitudinal clinical parameters, virus-specific T cell responses were assessed using Elispot, standard proliferative (carboxyfluorescein diacetate succinimidyl ester), and in vitro CD4(+) T cell assays. **RESULTS:** In all patients, anti-HCV treatment was started with pegylated interferon-alpha, and antiretroviral therapy was coadministered early during primary infection. HCV viremia was cleared under therapy with pegylated interferon-alpha in all 3 cases. In 2 patients, HIV replication was contained even after antiretroviral therapy had been interrupted, which was associated with strong HIV-specific CD8(+) and CD4(+) T cell responses. In these 2 patients, multispecific HCV CD4(+) T cell responses could also be detected. No HCV-specific CD4(+) T cell responses were detected in the third patient, who also had the lowest nadir CD4(+) cell count during primary HIV infection (<200 cells/microL). **CONCLUSIONS:** Anti-HIV and -HCV therapy should be considered early in cases of concomitant acute HCV and HIV coinfection, because successful therapy of HCV viremia seems possible even during primary HIV infection. HCV-specific T cell immunity is generated during primary HIV infection and can be preserved by HCV treatment. However, the optimal treatment algorithm needs to be established in prospective, randomized trials.

Viral interference between hepatitis B, C, and D viruses in dual and triple infections in HIV-positive patients. Morsica G, Bagaglio S, Cicconi P, et al. J Acquir Immune Defic Syndr. 2009 Aug;51(5):574-581.

http://www.ncbi.nlm.nih.gov/pubmed/19590432?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

OBJECTIVE: To investigate the reciprocal inhibitory effects of hepatitis B virus (HBV)/hepatitis C virus (HCV)/hepatitis D virus (HDV) infections in naive and previously antiretroviral-experienced HIV-positive patients. **DESIGN:** This retrospective study involved 72 consecutive patients of the Italian Cohort Naive Antiretroviral cohort: 21 coinfecting with HBV/HCV (group 1BC), 18 infected with HBV (group 2B), and 33 infected with HCV (group 3C). **METHODS:** Viral interference between HBV and HCV was assessed by means of the qualitative detection, quantification, and genotyping of each virus; HDV infection was assessed by means of genomic

amplification. **RESULTS:** Univariate analysis showed that HBV DNA was less frequently detected in group 1BC than in group 2B (16 of 21 vs 18 of 18; $P = 0.02$), their HBV load was significantly lower (median 3.9 vs 5.4 log₁₀ HBV DNA copies/mL; $P = 0.002$), and they more frequently carried HBV genotype D (12 of 13 vs 4 of 11; $P = 0.0071$). HCV RNA was less frequently detected in group 1BC than in group 3C (12 of 21 vs 33 of 33; $P < 0.0001$), and HDV RNA was more frequently detected in group 1BC than in group 2B (9 of 21 vs 2 of 18; $P = 0.028$). Multivariate analysis of the HBV-infected subjects showed that the risk of HCV coinfection was associated with older age [relative risk 0.28, 95% confidence interval (CI): 0.09 to 0.90; $P = 0.033$ for every 10 years older] and intravenous drug use (relative risk 73, 95% CI: 2.4 to >999.999; $P = 0.013$). The only predictor of HBV coinfection in HCV-infected individuals was a lower HCV load (relative risk 0.30, 95% CI: 0.11 to 0.79 for every additional log₁₀ HCV RNA; $P = 0.015$). **CONCLUSION:** HBV and HCV showed alternative dominant replication in the I.Co.N.A. cohort, with HBV having a more unfavorable effect on HCV replication.

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

Safe using messages may not be enough to promote behaviour change amongst injecting drug users who are ambivalent or indifferent towards death. Miller PG. Harm Reduct J. 2009 Jul 25;6(1):18. [Epub ahead of print]

Jul 25;6(1):18. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19630988?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: Health promotion strategies ultimately rely on people perceiving the consequences of their behaviour as negative. If someone is indifferent towards death, it would logically follow that health promotion messages such as safe using messages would have little resonance. This study aimed to investigate attitudes towards death in a group of injecting drug users (IDUs) and how such attitudes may impact upon the efficacy/relevance of 'safe using' (health promotion) messages. **METHODS:** Qualitative, semi-structured interviews in Geelong, Australia with 60 regular heroin users recruited primarily from needle and syringe programs. **RESULTS:** Over half of the interviewees reported having previously overdosed and 35% reported not engaging in any overdose prevention practices. 13% had never been tested for either HIV or hepatitis C. Just under half reported needle sharing of some description and almost all (97%) reported previously sharing other injecting equipment. Most interviewees reported being indifferent towards death. Common themes included; indifference towards life, death as an occupational hazard of drug use and death as a welcome relief. **CONCLUSIONS:** Most of the interviewees in this study were indifferent towards heroin-related death. Whilst interviewees were well aware of the possible consequences of their actions, these consequences were not seen as important as achieving their desired state of mind. Safe using messages are an important part of reducing drug-related harm, but people working with IDUs must consider the context in which risk behaviours occur and efforts to reduce said behaviours must include attempts to reduce environmental risk factors at the same time.

Visualizing hepatitis C virus infections in human liver by two-photon microscopy.

Liang Y, Shilagard T, Xiao SY, et al. Gastroenterology. 2009 Jul 23. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19632233?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND & AIMS: Although hepatitis C virus (HCV) is a common cause of cirrhosis and liver cancer, efforts to understand the pathogenesis of HCV infection have been limited by the low abundance of viral proteins expressed within the liver, which hinders the detection of infected cells

in situ. This study evaluated the ability of advanced optical imaging techniques to determine the extent and distribution of HCV-infected cells within the liver. **METHODS:** We combined 2-photon microscopy with virus-specific, fluorescent semi-conductor quantum dot probes to determine the proportion of hepatocytes that were infected with virus in frozen sections of liver tissue obtained from patients with chronic HCV infection. **RESULTS:** Viral core and NS3 antigens were readily detected in liver tissues from patients with chronic infection without confounding tissue autofluorescence. Specificity was confirmed by blocking with specific antibodies and by tissue co-localization of distinct viral antigens. Between 7% to 20% of hepatocytes were infected in patients with plasma viral RNA loads =10(5) IU/ml. Infected cells were in clusters, which suggested spread of the virus from cell to cell. Double-stranded RNA, a product of viral replication, was abundant within cells at the center of such clusters, but often scarce in cells at the periphery, consistent with more recent infection of cells in the center. **CONCLUSIONS:** Two-photon microscopy provides unprecedented sensitivity for detection of HCV proteins and dsRNA. Studies using this technology indicate that HCV infection is a dynamic process that involves a limited number of hepatocytes. HCV spread between cells is likely to be constrained by host responses.

Evaluation of the Abbott IUO RealTime HCV Assay and comparison to the Roche TaqMan HCV Analyte Specific Reagent. Pyne MT, Konnick EQ, Phansalkar A, Hillyard DR. J Clin Microbiol. 2009 Jul 22. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19625475?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The accurate and sensitive measurement of hepatitis C virus RNA is essential for the clinical management and treatment of infected patients and as a research tool for studying the biology of hepatitis C infection. We evaluated the linearity, reproducibility, precision, limit of detection, and concordance of viral genotype quantitation of the Abbott IUO RealTime HCV Assay (RealTime) using the Abbott m2000 platform, and compared the results to the Roche TaqMan Analyte Specific Reagent (TaqMan) and Bayer Versant HCV bDNA 3.0 assay (bDNA). Comparison of 216 samples analyzed by RealTime and TaqMan assays produced a Deming regression equation of RealTime = 0.940 (TaqMan) + 0.175 log₁₀ IU/mL. The average difference between the assays was 0.143 log₁₀ IU/mL, and was consistent across RealTime's dynamic range of nearly 7 log₁₀ IU/mL. There was no significant difference between genotypes among these samples. The limit of detection using eight replicates of the WHO HCV standard was determined to be 7.74 IU/mL by probit analysis. Replicate measurements of commercial genotype panels were significantly higher than TaqMan measurements for most samples and showed that the RealTime assay is able to detect all genotypes with no bias. Additionally, we showed that the amplicon generated by the widely used Roche COBAS Amplicor Hepatitis C Virus Test, version 2.0 can act as a template in the RealTime assay, but potential cross contamination could be mitigated by treatment with uracil-N-glycosylase (UNG). In conclusion, the RealTime assay accurately measured HCV viral loads over a broad dynamic range with no significant genotype bias.

Non-conventional transmission of hepatitis C: a true possibility ignored. Hyder Q, Burhan-ul-Haq M, Rashid R, Qazi S, Mehmood S, Hadi SF. J Pak Med Assoc. 2009 Jul;59(7):430-3.

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Hyder%20Q%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

OBJECTIVE: The exact mode of hepatitis C virus (HCV) transfer remains elusive in a vast majority of cases. We examined the possibility of non-conventional transmission of HCV by person-to-person contact. **METHOD:** A questionnaire based, prospective study was conducted at Pakistan Institute of Medical Sciences (PIMS) from July-October, 2006. Patients with compensated chronic

hepatitis B (CHB) &/or C (CHC) were registered for 6 month interferon (IFN) therapy. All candidates furnished information about age, gender and mode of transmission. The unanswered queries were interpreted as "missing data". After omission of cases with hepatitis B virus (HBV) infection alone, the remaining persons included in the present study were placed in: Group-A: Multifactorial transfer involving conventional (blood borne) and non-conventional modes; Group-B: Unifactorial transfer by non-conventional routes only; Group-C: No identifiable risk factor. Unlike conventional routes, the non-conventional modes represented likelihood of CHB &/or CHC by exposure to household contacts, to persons with hepatic cirrhosis and during traveling. **RESULTS:** Initially, 879 patients (mean age: 35.52 +/- 9.1 years) were registered. After exclusion of 25 subjects with HBV infection only, the remaining 854 were included. Of 854 cases, 830 (97.18%) were infected with HCV and 24 (2.81%) had co-infection with HBV & HCV. According to the mode(s) of transmission, Group-A: 515 (60.30%); Group-B: 136 (15.92%) and Group-C: 203 (23.77%) cases were identified. Dental treatment: 278 (32.55%) was the commonest conventional risk factor in Group-A. The non-conventional transfer of HCV in Group-A was mainly suggested by household contact: 222 (25.99%). Groups-A and -B combined, the sum of any non-conventional risk factor was comparable with and even higher than the leading haematogenous routes in Group-A. Groups-B and -C combined, HCV infection in 339 patients (39.69%) was apparently acquired by non-conventional modes, most probably by person-to-person interaction. **CONCLUSION:** Non-conventional transmission of HCV is a genuine possibility which is currently underestimated.

New and experimental therapies for HCV. Pereira AA, Jacobson IM. Nat Rev Gastroenterol Hepatol. 2009 Jul;6(7):403-11.

http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=Search&Term=%22Pereira%20A%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

Despite improvements to treatments for HCV infection, almost half of patients cannot be cured with standard combination therapy (pegylated interferon alpha and ribavirin). The HCV life cycle offers a number of potential targets for molecular therapy, and several specifically targeted antiviral therapies for HCV (STAT-Cs) are in preclinical and clinical stages of development. Evidence to date suggests that monotherapy with any antiviral drug is unlikely to eradicate HCV infection.

Combination therapy with interferon and ribavirin is necessary for the augmentation of antiviral drug activity and/or prevention of drug resistance. Results from clinical trials carried out in the past few years on STAT-C agents in combination with standard therapy with peginterferon and ribavirin provide great promise of higher rates of sustained virological response and, potentially, shorter duration of therapy than standard therapy alone achieves. Although pegylated interferon and ribavirin are likely to remain a cornerstone of therapeutic regimens in the short term, combinations of antiviral drugs of different classes, possibly along with novel agents that target host factors and modulate viral replication or augment antiviral defenses, offer the eventual possibility of interferon-free regimens.

Seroepidemiology of hepatitis C antibodies among dentists and their self-reported use of infection control measures. Ashkenazi M, Fisher N, Levin L, Littner MM. Community Dent Health. 2009 Jun;26(2):99-103.

http://www.ncbi.nlm.nih.gov/pubmed/19626741?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

OBJECTIVES: To determine the prevalence of hepatitis C virus (HCV) antibodies among dentists graduated from various countries and assess the use of infection control measures in their dental practice. **RESEARCH DESIGN:** The study included 301 Israeli dentists who attended an annual dental conference. Participants filled out a structured questionnaire regarding demographic (age,

gender, number of siblings, number of children) and occupational characteristics. Venous blood was examined for presence of HCV antibodies by enzyme immunoassay and confirmed by a third generation line immunoassay, which assesses antibodies to HCV-core antigens (INN-LIA HCV Ab III update, 100% sensitivity, 100% specificity). **RESULTS:** The prevalence of HCV antibodies among Israeli dentists was 1/301 (0.33%), similar to the prevalence range (0.1-0.5%) among the general Israeli population. The studied population included dentists (30.6%) who immigrated from Asia, Eastern Europe and the former USSR, where HCV prevalence ranges from 3.1% to 26.5%. Dentists routinely used gloves (99.6%), gown (93.3%), autoclaves (90.3%), dry heat (29.1%) and mask (81%). Dentists who graduated after 1985 used a mask or gown significantly more often than dentists who graduated before 1985 ($p < 0.001$ and $p = 0.004$, respectively). **CONCLUSION:** It seems that dentists who usually adhere to basic infection control measures are not at an increased risk for HCV.

Viral hepatitis in a homeless shelter in Hawai'i. Boyce DE, Tice AD, Ona FV, Akinaka KT, Lusk H. *Hawaii Med J.* 2009 Jun;68(5):113-5.

http://www.ncbi.nlm.nih.gov/pubmed/19583106?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

It is estimated that as many as 21,000 people in the state of Hawai'i may be infected with HCV. Most of those infected with viral hepatitis are unaware they are infected. Complications from viral hepatitis include liver cirrhosis and hepatocellular carcinoma. Hawai'i has the highest incidence of hepatocellular carcinoma in the United States. In 2003 there were over 6000 homeless and over 155,000 people at-risk of becoming homeless living in the state of Hawai'i. Risk factors for hepatitis, such as drug use, tattoos, sexual contact, and sharing of personal hygiene equipment are more prevalent in the homeless population. To determine the incidence of hepatitis B and C among a population of homeless individuals, a health fair was held at a Honolulu area homeless shelter with approximately 200 residents. The incidence of hepatitis B and C was determined by anti-HCV and HBsAg blood tests. A survey was also conducted regarding risk factors and basic demographics. Fifty-nine homeless adults volunteered for testing and took the survey. Thirty-one (52%) volunteers were born in Micronesia, twenty-four (41%) were born in the United States, two (3%) were born in Samoa, one (2%) was born in the Philippines, and one (2%) was born in the Marshall Islands. Forty adults were tested for Hepatitis C antibody, three of which tested positive. The primary risk factor among this group was jail time (100%), followed by illegal drug injection (67%), tattoos (67%), ear/body piercing (67%), snorting drugs (33%), blood transfusions (33%), and a sex partner with hepatitis (33%). Forty adults were also tested for HBsAg, One of which tested positive. This was a recent immigrant from Micronesia. Homeless people in Hawai'i are more likely to have hepatitis B or C because risk factors are common among this population. Additionally a large proportion of Hawai'i's homeless people come from the Pacific Islands, where the prevalence of hepatitis B is one of the highest in the world. In addition there are significant risks of hepatitis spread among the homeless and into the general population as many homeless do not realize they are infected. The health fair approach was an effective means for screening homeless people for hepatitis B and C. **Our preliminary information suggests** homeless shelters may be a good place for education, screening, and possibly interventions as well.

Living with hepatitis C and treatment: the personal experiences of patients. Sgorbini M, O'Brien L, Jackson D. *J Clin Nurs.* 2009 Aug;18(16):2282-91.

http://www.ncbi.nlm.nih.gov/pubmed/19583661?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

AIM: The purpose of the study was to explore the issues surrounding chronic hepatitis C, combination therapy and its impact on personal relationships to enhance understanding of the experiences of patients living with hepatitis C. This paper focuses on the experiences of the patients and their partners' experiences will be published separately. **BACKGROUND:** Patients with chronic hepatitis C who have active inflammatory changes on liver biopsy may undergo combination therapy with interferon and ribavirin. For some patients, the adverse effects of combination therapy are so severe that it can potentially place an enormous stress on personal relationships. **DESIGN:** The study was informed by Heideggerian phenomenology. **METHODS:** Purposive sampling and semi-structured interviews of five patients and their partners were conducted between 2004-2006 in Sydney Australia, to obtain a rich description of their experiences. **RESULTS:** The findings from this study revealed that chronic hepatitis C and combination therapy had an enormous impact on the lives of the patients, their partners and families. The illness and treatment had significant physiological effects that had an impact on quality of life; however, the social and psychological consequences of living with a highly stigmatised disease with an unknown course and outcome cannot be underestimated. **CONCLUSION:** The results of this study lend support to the effectiveness of providing equitable services to persons diagnosed with chronic hepatitis C. However, additional research is needed to explore gender, socioeconomic, sexual-orientation, transmission, cultural, religious and genotype differences in this group to address their needs better. **RELEVANCE TO CLINICAL PRACTICE:** Nurses play a significant role in educating patients with chronic hepatitis C, advocating for them and helping them to achieve a reasonable state of well being. Through deeper understanding of their experiences of illness and treatment, nurses can move beyond the medical oriented approach to care.