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CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

Pilot study of postexposure prophylaxis for hepatitis C virus in healthcare workers. Corey KE, Servoss JC, Casson DR, et al. Infect Control Hosp Epidemiol. 2009 Oct;30(10):1000-5.

http://www.ncbi.nlm.nih.gov/pubmed/19743901?itool=EntrezSystem2.PEntrez.Pubmed.PubmedRESULTSPanel.Pubmed_RVDocSum&ordinalpos=1

BACKGROUND AND OBJECTIVE: Hepatitis C virus (HCV) transmission occurs in 0.2%-10% of people after accidental needlestick exposures. However, postexposure prophylaxis is not currently recommended. We sought to determine the safety, tolerability, and acceptance of postexposure prophylaxis with peginterferon alfa-2b in healthcare workers (HCWs) exposed to blood from HCV-infected patients. **DESIGN:** Open-label pilot trial of peginterferon alfa-2b for HCV postexposure prophylaxis. **SETTING:** Two academic tertiary-referral centers. **METHODS:** HCWs exposed to blood from HCV-infected patients were informed of the availability of postexposure prophylaxis. Persons who elected postexposure prophylaxis were given weekly doses of peginterferon alfa-2b for 4 weeks. **RESULTS:** Among 2,702 HCWs identified with potential exposures to bloodborne pathogens, 213 (7.9%) were exposed to an HCV antibody-positive source. Of 51 HCWs who enrolled in the study, 44 (86%) elected to undergo postexposure prophylaxis (treated group). Seven subjects elected not to undergo postexposure prophylaxis (untreated group). No cases of HCV transmission were observed in either the treated or untreated group, and no cases occurred in the remaining 162 HCWs who did not enroll in this study. No serious adverse events related to a peginterferon alfa-2b regimen were recorded, but minor adverse events were frequent.

CONCLUSION: In this pilot study, there was a lower than expected frequency of HCV transmission after accidental occupational exposure. Although peginterferon alfa-2b was safe, because of the lack of HCV transmission in either the treated or untreated groups there is little evidence to support routine postexposure prophylaxis against HCV in HCWs.

Impact of high-dose peginterferon alfa-2A on virological response rates in patients with hepatitis C genotype 1: a randomized controlled trial. Roberts SK, Weltman MD, Crawford DH, et al. Hepatology. 2009 Oct;50(4):1045-55.

http://www.ncbi.nlm.nih.gov/pubmed/19676125?itool=EntrezSystem2.PEntrez.Pubmed.PubmedRESULTSPanel.Pubmed_RVDocSum&ordinalpos=1

This study tested the hypothesis that high-dose peginterferon alfa-2a (PEG-IFNalpha-2a) for the first 12 weeks would increase early and sustained virological response (SVR) rates in patients with chronic hepatitis C genotype 1. Eight hundred ninety-six patients were randomized 1:1 to 360 microg (n = 448) or 180 microg (n = 448) PEG-IFNalpha-2a weekly plus ribavirin at 1000-1200 mg/day for 12 weeks, followed by 36 weeks of 180 microg PEG-IFNalpha-2a weekly plus ribavirin

at 1000-1200 mg/day with 871 patients evaluable for the intention-to-treat analysis. Virological responses were assessed by TaqMan (limit of detection 15 IU/mL) at week 4, 8, 12, 24, 48 (end of therapy), and 24 weeks following therapy (SVR). Undetectable hepatitis C virus RNA rates were significantly higher among patients receiving high-dose induction therapy at week 4 (36% versus 26%, $P < 0.005$), week 8 (61% versus 50%, $P < 0.005$), and week 12 (74% versus 62%, $P < 0.005$). However, SVR was not significantly different between patients receiving high-dose (53%) and standard (50%) therapy. Significant baseline prognostic factors for SVR included age, sex, race, histological stage, and viral load. SVR was considerably higher among patients with no or minimal fibrosis (64% and 60%, respectively) compared to those with severe fibrosis/cirrhosis (28% and 24%, respectively). The frequency of serious adverse events and drug discontinuations were similar in both groups, whereas PEG-IFN dose modification, weight and appetite reduction, and grade IV neutropenia were significantly higher in the induction arm. **CONCLUSION:** Induction dosing with 360 microg/week PEG-IFNalpha-2a for 12 weeks was well tolerated and enhanced early virological response but not SVR rates. The high SVR rates in patients with minimal fibrosis highlight the benefit of early treatment in patients with hepatitis C virus genotype 1.

Equally poor outcomes to pegylated interferon-based therapy in African Americans and Hispanics with chronic hepatitis C infection. Satapathy SK, Lingisetty CS, Proper S, Chaudhari S, Williams S. J Clin Gastroenterol. 2009 Oct 12. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19826275?itool=EntrezSystem2.PEntrez.Pubmed.PubmedRESULTSPanel.Pubmed_RVDocSum&ordinalpos=1

OBJECTIVES: Treatment response to pegylated interferon based regimen is different between African Americans and Whites, but little comparable data is available comparing Hispanics and African Americans. **PATIENTS:** We retrospectively evaluated the rate of success in the treatment completion and response to peginterferon alpha-2a or alpha-2b plus ribavirin in 103 (male:female-69:34) hepatitis C virus (HCV)-polymerase chain reaction positive patients that included 68 Hispanic and 35 African Americans. **METHODS:** Patients were treated with peginterferon alpha-2a 180 mcg/wk ($n=25$) or peginterferon alpha-2b 1.5 mcg/kg/wk ($N=78$) and ribavirin 1000 to 1200 mg/d for 24 weeks (genotype 2 and 3) or 48 weeks (genotype 1 and 4) based on the genotype of the patient. Treatment was discontinued if the patients failed to have a 2-log drop in viral load after 12 weeks of treatment. Primary aim of the study was to evaluate success in completing a scheduled duration of pegylated interferon and ribavirin treatment in patients with chronic HCV infection and the reasons for discontinuation of the treatment. The secondary aim was to look for the end of treatment virologic response and sustained virologic response. The analysis was conducted by intention-to-treat. **RESULTS:** Of the 103 patients included in the study, 50 (48.5%) patients dropped out of the treatment because of side effects of the drug or noncompliance to the treatment protocol or alternate reasons; 44 (42.7%) of them could not continue beyond 12 weeks of therapy. There were no significant differences in the drop out rate between the African American [15 (43%)] and Hispanic [35 (51.5%)] patients ($P=0.410$). Overall, 41% of the patients completed the scheduled 24 week or 48 week treatment. HCV genotype-1 was the most prevalent genotype in both African Americans and Hispanics (88.6% vs. 75%, $P=0.107$). Overall end of the treatment response (ETR) was 29.1% (30/103) and sustained virologic response (SVR) was 23.3% (24/103) in this population. No significant differences were noted in the ETR (20% vs. 34%, $P=0.146$) and the SVR (20% vs. 25%, $P=0.572$) between the African Americans and Hispanics. When data were analyzed by genotype, overall SVR rates were 14.6% (12/82) in genotype 1 versus 57% (12/21) in genotype 2/3/4 ($P<0.0001$). Both these ethnic groups had comparable response rates when only patients with genotype-1 were considered 5/31 (16.1%) versus 7/51 (13.7%, $P=0.767$). **CONCLUSIONS:** A significant proportion of the African Americans and Hispanics referred for HCV treatment with pegylated interferon dropped out early in the therapy, suggesting possible racial, socioeconomic, and cultural barriers in successful treatment for chronic HCV infection. Overall, both groups had similar

poor response rates, well below those reported for White patients. As is true for the general population, patients with nongenotype 1 infection had a significantly better ETR and SVR.

Gene profiling, biomarkers and pathways characterizing HCV-related hepatocellular carcinoma. De Giorgi V, Monaco A, Worchech A, et al. *J Transl Med.* 2009 Oct 12;7(1):85. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19821982?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_RESULTSPanel.Pubmed_RVDocSum&ordinalpos=1

BACKGROUND: Hepatitis C virus (HCV) infection is a major cause of hepatocellular carcinoma (HCC) worldwide. The molecular mechanisms of HCV-induced hepatocarcinogenesis are not yet fully elucidated. Besides indirect effects as tissue inflammation and regeneration, a more direct oncogenic activity of HCV can be postulated leading to an altered expression of cellular genes by early HCV viral proteins. In the present study, a comparison of gene expression patterns has been performed by microarray analysis on liver biopsies from HCV-positive HCC patients and HCV-negative controls. **METHODS:** Gene expression profiling of liver tissues has been performed using a high-density microarray containing 36'000 oligos, representing 90% of the human genes. Samples were obtained from 14 patients affected by HCV-related HCC and 7 HCV-negative non-liver-cancer patients, enrolled at INT in Naples. Transcriptional profiles identified in liver biopsies from HCC nodules and paired non-adjacent non-HCC liver tissue of the same HCV-positive patients were compared to those from HCV-negative controls by the Cluster program. The pathway analysis was performed using the BRB-Array-Tools based on the "Ingenuity System Database". Significance threshold of t-test was set at 0.001. **RESULTS:** Significant differences were found between the expression patterns of several genes falling into different metabolic and inflammation/immunity pathways in HCV-related HCC tissues as well as the non-HCC counterpart compared to normal liver tissues. Only few genes were found differentially expressed between HCV-related HCC tissues and paired non-HCC counterpart. **CONCLUSION:** In this study, informative data on the global gene expression pattern of HCV-related HCC and non-HCC counterpart, as well as on their difference with the one observed in normal liver tissues have been obtained. These **RESULTS** may lead to the identification of specific biomarkers relevant to develop tools for detection, diagnosis, and classification of HCV-related HCC.

Adjuvant therapy used in conjunction with combination therapy for chronic hepatitis C improves sustained virus response rates in genotype 1 patients. Cash WJ, Patterson K,

Callender ME, McDougall NI. *J Viral Hepat.* 2009 Oct 11. [Epub ahead of print]

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

Combination treatment with pegylated interferon (Peg-IFN) and ribavirin remains the gold standard in the treatment of chronic hepatitis C. This therapy is limited by many side-effects including anaemia, neutropenia and reduced quality of life. The use of adjuvant agents to reduce the frequency of dose reductions because of haematological side-effects has been proven to be effective but there are few reports of what effect the use of these adjuvant therapies is having on sustained virological response (SVR). The aim of the study was to assess the clinical impact on sustained virological response of adjuvant therapies during combination therapy with Peg-IFN and ribavirin for chronic hepatitis C. A total of 132 patients, 96 males, were included in the study. The overall SVR was 66.7%, with 50% of genotype 1/4/6 (n = 27/54) patients achieving SVR and 78.2% of genotypes 2/3. The overall SVR of the treatment naïve patients (83/121) was 68.6%. Fifty-one of these patients were genotype 1 with 49.0% (25/51) of this group achieving SVR. The genotype 2/3 group of treatment naïve patients reached an SVR of 82.9% (58/70). Adjuvant therapy was used in 57 patients (43.8%). With the use of supportive adjuvant therapy, we achieved an overall SVR of 66.7% and in treatment naïve patients 68.6%. In genotype 1 patients, SVR rates of up to 46% have been

reported in previous studies without the use of erythropoietin and granulocyte colony stimulating factor. We have demonstrated the SVR for genotype 1 can be improved to 50% overall.

Maintenance ribavirin monotherapy delays fibrosis progression in liver transplant recipients with recurrent hepatitis C at high risk of progression. Lionetti R, Tisone G, Palmieri G, et al. Dig Liver Dis. 2009 Oct 7. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19818696?itool=EntrezSystem2.PEntrez.Pubmed.PubmedRESULTSPanel.Pubmed_RVDocSum&ordinalpos=1

BACKGROUND: Fibrosis in liver transplant recipients with recurrent HCV is fast, yet, different patterns of progression are recognized. **AIMS:** To investigate histological findings associated with maintenance ribavirin monotherapy in patients with recurrent HCV transplanted ≥ 4 years earlier. **METHODS:** 14 recipients at high risk of progression (fibrosis progression rate > 0.33 units/year and/or persistently elevated ALT) were assigned to receive ribavirin for 3 years. 11 patients at lower risk of progression (FPR ≤ 0.33 units/year and normal ALT) as controls. Biopsies were obtained yearly since transplant and 7 consecutive biopsies were evaluated. **RESULTS:** Improved necroinflammation (reduction ≥ 2 grading) was observed in 7 treated with ribavirin and 3 untreated patients, while 1 and 3 patients worsened respectively. Fibrosis improved (reduction > 1 staging) in 2 ribavirin-treated patients, unchanged in 10 and worsened (increase ≥ 1 staging) in 2. Fibrosis progression decreased from 0.48 ± 0.27 observed during the 3-year pre-treatment period to 0.04 ± 0.31 units/year ($p=0.003$) during the 3 years of ribavirin. Among untreated fibrosis remained unchanged in 1 and worsened in 10 ($p<0.001$), yearly fibrosis progression rate increasing from 0.15 ± 0.17 units/year to 0.42 ± 0.39 units/year ($p=0.10$). **CONCLUSIONS:** Maintenance ribavirin monotherapy delays fibrosis progression in high risk patients, offering an alternative strategy for those failing to respond to conventional treatment.

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. 2009 Oct 26. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19858727?itool=EntrezSystem2.PEntrez.Pubmed.PubmedRESULTSPanel.Pubmed_RVDocSum&ordinalpos=1

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.

Pegylated interferon alpha2b versus pegylated interferon alpha2a for chronic hepatitis C:

The unreached goal of superiority. Rumi MG. *J Hepatol.* 2009 Oct 2. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19853954?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_RESULTSPanel.Pubmed_RVDocSum&ordinalpos=1

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 mg per kilogram of body weight per week or a low dose of 1.0 mg 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 mg 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.

Rapid HCV-RNA decline with once-daily TMC435: A Phase I study in healthy volunteers and hepatitis C patients.

Reesink HW, Fanning GC, Abou Farha K, et al. *Gastroenterology.* 2009 Oct 20. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19852962?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_RESULTSPanel.Pubmed_RVDocSum&ordinalpos=1

BACKGROUND: The search for targeted anti-HCV drugs is driven by the side-effect profile and limited efficacy of the current standard of care (pegylated interferon-alpha/ribavirin). In a first-in-human trial, we tested the safety, tolerability and pharmacokinetics of the macrocyclic HCV NS3/4A protease inhibitor TMC435 in healthy volunteers, followed by HCV-genotype-1-infected patients to assess antiviral activity. **METHODS:** The TMC435350-C101 study was a Phase I, randomized, double-blind, placebo-controlled trial in 49 healthy volunteers, followed by an open-label, non-placebo-controlled panel in six genotype 1 hepatitis C patients. Healthy volunteers received oral single ascending doses (up to 600 mg) or 5-day multiple ascending doses (200 mg twice-daily, 100, 200 or 400 mg once-daily). Patients received 200 mg once-daily for 5 days. Pharmacokinetics and safety were evaluated for all panels and plasma HCV-RNA levels were

determined in patients. **RESULTS:** There were no serious adverse events, no grade 3 reactions and no treatment-related discontinuations; pharmacokinetics supported a once-daily dosing regimen. Plasma HCV-RNA levels dropped rapidly in all patients, with a median maximal reduction of 3.9 log(10) IU/mL, and a median of 6 days to maximal reduction. The initial steep reduction of HCV-RNA (median 3.5 log(10) IU/mL at Day 3) was followed by a more gradual decline that was maintained over the dosing period. No viral breakthroughs (>1 log(10) IU/mL HCV-RNA increase from nadir) were observed during treatment, nor in the 3 days post-treatment; HCV-RNA returned to pre-treatment levels by Week 4. **CONCLUSIONS:** Once-daily TMC435 given orally was generally safe and well tolerated, and demonstrated potent antiviral activity.

Therapeutic effects of pegylated interferon plus ribavirin in chronic hepatitis C patients with occult hepatitis B virus dual infection. Chen LW, Chien RN, Yen CL, Chang JJ, Liu CJ, Lin CL. J Gastroenterol Hepatol. 2009 Oct 9. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19817959?itool=EntrezSystem2.PEntrez.Pubmed.PubmedRESULTSPanel.Pubmed_RVDocSum&ordinalpos=1

BACKGROUND AND AIM: Occult hepatitis B virus (HBV) infection is defined by the detectable serum HBV-DNA in HBV surface antigen-negative patients. This retrospective study **AIMS** to evaluate the therapeutic effects of combined pegylated interferon (PEG-IFN) plus ribavirin (RBV) in patients with concurrent occult HBV/hepatitis C virus (HCV) dual infection. **METHODS:** In total, 126 consecutive chronic hepatitis C (CHC) patients who received combined PEG-IFN and RBV therapy were included. Patients were divided into the occult HBV/HCV dual infection group or the HCV-monoinfected group according to whether or not they had the detectable serum HBV-DNA. The biochemical and virological responses to combined therapy were compared between these two groups. Serum HCV-RNA and HBV-DNA were checked before treatment, at the end of treatment as well as at 6- and 12-months' follow up in the occult HBV/HCV group. **RESULT:** Six patients were seropositive for HBV-DNA and were included in the occult HBV/HCV dual infection group. There were no statistical differences in the biochemical and virological responses to combined therapy between these two groups. Undetectable serum HBV-DNA was noted at the end of the treatment and the 6- and 12-months' follow up in patients with occult HBV/HCV dual infection. **CONCLUSION:** Occult HBV infection in CHC patients is rare. The biochemical and virological responses to combined PEG-IFN and RBV therapy might be similar in CHC patients with or without occult HBV infection. The serum HBV-DNA level was low in patients with occult HBV/HCV dual infection who responded to combined therapy.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Hepatitis c virus ns3 protease inhibitors: large, flexible molecules of peptide origin shows satisfactory permeability across caco-2 cells. Bergström CA, Bolin S, Artursson P, Rönn R, Sandström A. Eur J Pharm Sci. 2009 Oct 12

http://www.ncbi.nlm.nih.gov/pubmed/19833201?itool=EntrezSystem2.PEntrez.Pubmed.PubmedRESULTSPanel.Pubmed_RVDocSum&ordinalpos=1

The purpose of this study was to investigate the intestinal absorption of tripeptide-based compounds intended for treatment of Hepatitis C Virus (HCV) infection. The intestinal permeability of eleven HCV NS3 protease inhibitors (Mw 687-841, ClogD(pH7.4) 1.2-7.3 and 10-13 hydrogen bond donors/acceptors) were measured using Caco-2 cells. Each compound was investigated in the apical to basolateral (a-b) and basolateral to apical (b-a) direction at pH 7.4. For compounds displaying efflux the experiment was repeated in the presence of 1µM GF120918 to investigate possible involvement of P-glycoprotein (Pgp; ABCB1). All compounds displayed intermediate to high permeability. Seven of them showed extensive efflux, with 31 to 114-fold higher permeability in the b-a direction than the a-b. Addition of the Pgp inhibitor GF120918

reduced the b-a transport rate for the effluxed compounds. However, for inhibitors with a C-terminal carboxylic acid and the acidic bioisosteres thereof the efflux was still significant. Hence, the negative charge resulted in efflux by other ABC-transporters than Pgp. **From this study it can be concluded** that small changes in the overall structure can lead to a large variation in permeability and efflux as shown by the inhibitors herein, properties that also may influence the resulting inhibition potency of the compounds when performing cell-based pharmacological assays.

Determinants of hepatitis C virus nonstructural protein 2 protease domain required for production of infectious virus. Dentzer TG, Lorenz IC, Evans MJ, Rice CM. J Virol. 2009 Oct 7. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19812162?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_RESULTSPanel.Pubmed_RVDocSum&ordinalpos=1

The hepatitis C virus (HCV) non-structural protein 2 (NS2) is a dimeric multifunctional hydrophobic protein with an essential but poorly understood role in infectious virus production. We investigated the determinants of NS2 function in the HCV life cycle. Based on the crystal structure of the post-cleavage form of the NS2 protease domain, we mutated conserved features and analyzed the effects of these changes on polyprotein processing, replication, and infectious virus production. We found that mutations around the protease active site inhibit viral RNA replication, likely by preventing NS2-3 cleavage. In contrast, alterations at the dimer interface or in the C-terminal region did not affect replication, NS2 stability, or NS2 protease activity, but decreased infectious virus production. A comprehensive deletion and mutagenesis analysis of the C-terminal end of NS2 revealed the importance of its C-terminal leucine residue in infectious particle production. The crystal structure of the NS2 protease domain shows that this C-terminal leucine is locked in the active site, and mutation or deletion of this residue could therefore alter the conformation of NS2 and disrupt potential protein-protein interactions important for infectious particle production. These studies begin to dissect the residues of NS2 involved in its multiple essential roles in the HCV life cycle and suggest NS2 as a viable target for HCV-specific inhibitors.

Anti-hepatitis C virus activity of novel beta-d-2'-C-methyl-4'-azido pyrimidine nucleoside phosphoramidate prodrugs. Rondla R, Coats SJ, McBrayer TR, et al. Antivir Chem Chemother. 2009 Oct 19;20(2):99-106.

http://www.ncbi.nlm.nih.gov/pubmed?term=%22Rondla%20R%22%5BAuthor%5D&itool=Email.EmailReport.Pubmed_ReportSelector.Pubmed_RVAbstract

BACKGROUND: 2'-C-methyl and 4'-azido nucleosides have previously demonstrated inhibition of hepatitis C virus (HCV) replication by targeting the RNA-dependent RNA polymerase NS5B. In an effort to discover new and more potent anti-HCV agents, we envisioned synthesizing nucleoside analogues by combining the 2'-C-methyl-moiety with the 4'-azido-moiety into one molecule.

METHODS: 2'-C-methyl-4'-azido pyrimidine nucleosides were synthesized by first converting 2'-C-methyl ribonucleosides to the corresponding 4'-exocyclic methylene nucleosides. Treatment with iodine azide, benzylation of the 2'- and 3'-hydroxy groups, oxidative displacement of the 5'-iodo group with meta-chloroperoxybenzoic acid, and debenylation gave the desired 2'-C-methyl-4'-azido uridine and thymidine analogues in good yield. Standard conversion of uridine to cytidine via the 4-triazole yielded 2'-C-methyl-4'-azido cytidine. In addition, 5'-phosphoramidate derivatives of 2'-C-methyl-4'-azido uridine and cytidine were synthesized to bypass the initial phosphorylation step.

RESULTS: The prepared nucleosides and their 5'-monophosphate prodrugs were evaluated for their ability to inhibit replication of the hepatitis C virus in a subgenomic replicon cell based assay. Cytotoxicity in Huh7 cells was determined simultaneously with anti-HCV activity by extraction and amplification of both HCV RNA and ribosomal RNA. Among the newly synthesized compounds, only the 5'-monophosphate nucleoside prodrugs had modest and selective anti-HCV activity. All prepared pyrimidine nucleosides and 5'-monophosphate nucleoside prodrugs displayed no evidence

of cytotoxicity at high concentrations. **CONCLUSIONS:** This work is the first example of both inactive uridine and cytidine analogues of a nucleoside being converted to active anti-HCV nucleosides via 5'-monophosphate prodrugs.

Relation between body fat and liver fat accumulation and cytokine pattern in non-alcoholic patients with chronic HCV infection. González-Reimers E, Castellano-Higuera A, Alemán-Valls R, et al. *Ann Nutr Metab.* 2009 Oct 23;55(4):351-357. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19851063?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_RESULTSPanel.Pubmed_RVDocSum&ordinalpos=1

BACKGROUND: Liver steatosis in chronic hepatitis C virus (HCV) infection is multifactorial. Therefore, there is not necessarily a relation between obesity and liver fat. On the other hand, body fat secretes cytokines, and cytokines and oxidative damage play important roles on progression of liver disease. **METHODS:** We analyzed the relationships between liver fat (assessed by histomorphometry) and trunk and subcutaneous fat (waist perimeter, triceps skinfold, BMI); the relationships between liver and body fat and cytokines (IL-6, TNF-alpha, IL-8, IFN-gamma, IL-4), adipokines (adiponectin and TIMP-1), and serum malondialdehyde and antioxidants (glutathione peroxidase and superoxide dismutase (SOD) activities); and the relationships of these data with histological changes in 40 HCV-infected non-alcoholic patients. **RESULTS:** Significant correlations were found between liver fat and waist perimeter and BMI, and between serum TIMP-1 and liver fat. Serum TIMP-1 was significantly related to body fat stores; serum IL-6 and IFN-gamma were related to histological inflammation. Patients with waist perimeter >102 cm (men) or 88 cm (women) showed increased liver fat. In 38.8% of non-obese patients, liver fat accumulation was intense. **CONCLUSIONS:** There is a relationship between visceral fat, serum TIMP-1 and liver steatosis. However, at least in some patients, factors different from mere adiposity play a role in liver steatosis.

Real-time quantitative assay for routine testing HCV RNA in formalin-fixed, paraffin-embedded liver samples. Gruppioni E, Vasuri F, Fiorentino M, et al. *Diagn Mol Pathol.* 2009 Oct 26. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19861893?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_RESULTSPanel.Pubmed_RVDocSum&ordinalpos=1

The assessment of hepatitis C virus (HCV) RNA in liver tissues is clinically relevant in cases where histology, liver function tests, and HCV serology are not sufficient for a definitive diagnosis of HCV-related hepatitis. We analyzed 215 formalin-fixed, paraffin-embedded liver needle biopsies from patients infected with HCV genotypes 1b and 2. HCV RNA extracted from paraffin sections were quantified by means of a TaqMan real-time reverse transcription-polymerase chain reaction method. The quantification of HCV RNA in liver tissue was correlated with the amount of HCV detected by immunohistochemistry (IHC) on paired frozen biopsies, the HCV RNA load in the serum, and the main serum tests of liver function and cholestasis. HCV RNA was detected by real-time reverse transcription-polymerase chain reaction in 169 liver biopsies (78.6%) with a mean value of 13.59+/-37.25 IU/ng. Tissue HCV RNA levels strongly correlated with the IHC **RESULTS** ($P<0.001$, Spearman test), HCV serum load ($P<0.001$), aspartate aminotransferase ($P=0.001$), gamma-glutamyl transpeptidase ($P=0.012$), and aspartate aminotransferase/alanine aminotransferase ratio ($P=0.029$). HCV RNA was amplified in up to 7-year-old archival tissue samples. Real-time HCV RNA quantification on archival liver tissue may be clinically relevant in case of "occult" HCV infection or for the diagnosis of patients with known HCV infection and hepatic dysfunction but seronegative for HCV RNA. The assessment of the levels of HCV RNA in the liver might also be important for monitoring the effectiveness of antiviral therapy and the progression of disease in patients with chronic HCV hepatitis.

ISG15, a ubiquitin-like interferon stimulated gene, promotes Hepatitis C Virus production in vitro: Implications for chronic infection and response to treatment. Chen L, Sun J, Meng L, Heathcote J, Edwards A, McGilvray I. *J Gen Virol.* 2009 Oct 21. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/19846672?ordinalpos=5&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_RESULTSPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND & AIMS: Up-regulation of interferon stimulated genes (ISGs), including interferon stimulated gene 15 (ISG15) and other members of the ISG15 pathway, in pre-treatment liver tissue of Hepatitis C virus (HCV) chronically-infected patients is associated with subsequent treatment failure (pegylated interferon-alpha/ribavirin, pegIFN/rib). Here, we study the effect of ISG15 on HCV production in vitro. **METHODS:** The levels of ISG15 and of its conjugation to target proteins (ISGylation) were increased by plasmid transfection, or ISGylation was inhibited by siRNA directed against the E1 activating enzyme Ube1L in Huh7.5 cells. Cells were infected with HCV J6/JFH1 virus, and HCV RNA and viral titers determined. **RESULTS:** Levels of both HCV RNA and virus increased when levels of ISG15 and ISGylation were increased, and decreased when ISGylation was inhibited. The effects of ISGylation on HCV are independent of upstream IFN signaling: IFNalpha-induced ISG expression is not altered by Ube1L knockdown. The effect is also not likely secondary to a cytokine effect: treatment of cells with purified ISG15 does not inhibit HCV production. **CONCLUSIONS:** Although ISG15 has antiviral activity against most viruses, ISG15 promotes HCV production. HCV might exploit ISG15 as a host immune evasion mechanism, and this may in part explain how increased expression of ISGs, especially ISG15, correlates with subsequent interferon-based treatment failure.

HIV/HCV COINFECTION

Prevalence, incidence and risk factors for hepatitis C in homosexual men: Data from two cohorts of HIV negative and HIV positive men in Sydney, Australia. Jin F, Prestage GP, Matthews GV, et al. *Sex Transm Infect.* 2009 Oct 19. [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/19841003?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_RESULTSPanel.Pubmed_RVDocSum&ordinalpos=1

BACKGROUND: An increasing incidence of hepatitis C virus (HCV) infection in HIV positive homosexual men has recently been described, but it is uncertain to what extent this reflects sexual transmission. We report prevalence, incidence and risk factors for HCV infection in community-based cohorts of HIV negative and HIV positive homosexual men in Sydney. **METHODS:** Both cohorts recruited participants using similar community-based strategies. Men underwent annual face-to-face interviews, and reported history of injecting drug use (IDU) and sexual and other behaviours that might lead to blood contact. HCV screening was offered to consenting participants from 2001 to 2007. **RESULTS:** At baseline, HCV prevalence was 1.07% in the HIV negative and 9.39% in the HIV positive men. HCV seropositivity was strongly associated with a history of IDU in both cohorts (OR=56.18, 95% CI 12.55-251.5 in HIV negative, and OR=24.46, 95% CI 5.44-110.0 in HIV positive). In the HIV negative cohort, five men seroconverted to HCV over 4412.1 person-years of follow-up, an incidence of 0.11 per 100 person-years (95% CI 0.03-0.26). Only one seroconverter reported IDU. Of the five, four reported sexual contact with HIV positive men (HR=8.23, 95% CI 0.91-74.28) and two had an incident ulcerative sexually transmitted infection. In the HIV positive cohort, none seroconverted over 238.1 person-years of follow-up (97.5% CI 0-1.54, single-sided). **CONCLUSION:** HCV prevalence was almost ten times higher in HIV positive homosexual men. Although incident HCV infection was uncommon in both cohorts, cases of non-IDU related transmission did occur, possibly linked to sexual contact with HIV positive men.

Long-term outcome of hepatitis B and hepatitis C virus co-infection and single HBV infection acquired in youth. Zampino R, Marrone A, Merola A, et al. J Med Virol. 2009 Oct 25;81(12):2012-2020. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19856471?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_RESULTSPanel.Pubmed_RVDocSum&ordinalpos=1

Co-infection with HBV and HCV seems to be associated with more severe liver disease in retrospective and cross-sectional studies in adults, but no data are available when co-infection is acquired in youth. The long-term outcome of infection acquired in youth was assessed in patients co-infected with HBV and HCV and in patients with HBV infection only. Twenty-seven patients with HBV and HCV co-infection and 27 patients infected with HBV only were enrolled. Seventy-six per cent of the patients were treated with alpha-interferon for 1 year. After a median follow-up of 23 years, the annual progression rate of fibrosis was 0.07 in patients co-infected with HBV and HCV, and in those infected with HBV it was 0.07 and 0.11 ($P < 0.004$) for HBe and anti-HBe-positive patients, respectively. In co-infected patients, the development of cirrhosis was observed in 2 (7.4%) and of hepatocellular carcinoma (HCC) in 1 (3.7%), while in those with HBV, cirrhosis appeared in one patient (3.7%). Alcohol intake (OR = 9.5 +/- 1.2; 95% CI = 6.6-13.9; $P < 0.0001$) was independently associated with cirrhosis and HCC. alpha-interferon showed no efficacy during treatment, but the treated group showed higher HCV RNA clearance during post-treatment follow-up. Co-infection with HBV and HCV and single HBV infection acquired in youth showed a low rate of progression to liver fibrosis, no liver failure, and low development of HCC during a median follow-up of 23 years (range 17-40).

Meta-analysis: increased mortality associated with hepatitis C in HIV-infected persons is unrelated to HIV disease progression. Chen TY, Ding EL, Seage Iii GR, Kim AY. Clin Infect Dis. 2009 Oct 20. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19842982?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_RESULTSPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: It is unclear whether coinfection with hepatitis C virus (HCV) increases mortality in patients with human immunodeficiency virus (HIV) infection during the era of highly active antiretroviral therapy (HAART). With use of a meta-analysis, we estimated the effect of HCV infection on HIV disease progression and overall mortality in the pre-HAART and HAART eras. **METHOD:** The PubMed and EMBASE databases were searched for studies published through 30 April 2008. Additional studies were identified from cited references. Studies reporting disease progression or mortality among HCV-HIV coinfecting patients were selected. Cross-sectional studies, studies without HCV-negative control subjects, and studies involving children and/or patients who had undergone liver transplantation were excluded. Two authors reviewed articles and extracted data on the demographic characteristics of study populations and risk estimates. Meta-regression was used to explore heterogeneity. **RESULTS:** Ten studies from the pre-HAART era and 27 studies from the HAART era were selected. In the pre-HAART era, the risk ratio for overall mortality among patients with HCV-HIV coinfection, compared with that among patients with HIV infection alone, was 0.68 (95% confidence interval [CI], 0.53-0.87). In the HAART era, the risk ratio was 1.12 (95% CI, 0.82-1.51) for AIDS-defining events and 1.35 (95% CI, 1.11-1.63) for overall mortality among coinfecting patients, compared with that among patients with HIV monoinfection. **CONCLUSIONS:** HCV coinfection did not increase mortality among patients with HIV infection before the introduction of HAART. In contrast, in the HAART era, HCV coinfection, compared with HIV infection alone, increases the risk of mortality, but not the risk of AIDS-defining events. Future studies should determine whether successful treatment of HCV infection could reduce this excess risk of mortality in coinfecting patients.

HCV/HIV co-infection in hemophiliacs: high rates of sustained virological response to pegylated interferon and ribavirin therapy. Mancuso ME, Rumi MG, Aghemo A, et al. *J Thromb Haemost.* 2009 Oct 3. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19799716?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_RESULTSPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND: Progression of chronic hepatitis C virus (HCV) infection to end-stage liver disease is accelerated in patients co-infected with the human immunodeficiency virus (HIV). HCV/HIV co-infected hemophiliacs are no exception. While eradication of HCV with pegylated interferon (Peg-IFN) plus ribavirin (Rbv) is the only approach to halt progression of liver disease, the rates of sustained virological response (SVR) in co-infected patients are attenuated compared to HCV mono-infected patients. Nonetheless in HCV infected hemophiliacs, considered a difficult-to-treat population, current treatment strategies yielded rates of SVR similar to those obtained in non-hemophiliacs. **OBJECTIVES AND PATIENTS:** In this open-label, prospective, multicenter study, the efficacy and safety of therapy with Peg-IFNalpha2a plus Rbv was evaluated in 34 HCV/HIV co-infected adult hemophiliacs naïve to previous antiviral therapy. **METHODS:** Peg-IFNalpha2a was administered at a dose of 180 mug subcutaneously once weekly plus oral Rbv 1000-1200 mg/day for 48 weeks irrespective of HCV genotype. **RESULTS:** All but one patients (3%) completed the study, 15 (44%) achieved a SVR and 13 (38%) required dose reduction of either drug. A rapid virological response (HCV-RNA clearance at week 4; $p=0.01$), a complete early virological response (HCV-RNA clearance at week 12; $p=0.005$), and absence of cirrhosis ($p=0.04$), were independent predictors of SVR. During a median post-treatment follow-up of 3 years, a steady increase of CD4(+) cell count and CD4(+)/CD8(+) cell ratio was observed in SVR patients. **CONCLUSIONS:** These **RESULTS** strongly encourage anti-HCV therapy in HCV/HIV co-infected hemophiliacs.

Enfuvirtide: a safe and effective antiretroviral agent for human immunodeficiency virus-infected patients shortly after liver transplantation. Teicher E, Abbara C, Duclos-Vallée JC, et al. *Liver Transpl.* 2009 Oct;15(10):1336-42.

http://www.ncbi.nlm.nih.gov/pubmed/19790146?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_RESULTSPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

The aim of this study was to evaluate the impact of an enfuvirtide-based antiretroviral (ARV) regimen on the management of immunosuppression and follow-up in hepatitis C virus (HCV)/hepatitis B virus (HBV)/human immunodeficiency virus (HIV)-coinfected liver transplant patients in comparison with a lopinavir/ritonavir-based ARV regimen. Tacrolimus and cyclosporine trough concentrations were determined at a steady state during 3 periods: after liver transplantation without ARV treatment (period 1), at the time of ARV reintroduction (period 2), and 2 to 3 months after liver transplantation (period 3). The findings for 22 HIV-coinfected patients were compared (18 with HCV and 4 with HBV); 11 patients were treated with enfuvirtide and were matched with 11 lopinavir/ritonavir-exposed patients. During period 1, tacrolimus and cyclosporine A doses were 8 and 600 mg/day, respectively, and the trough concentrations were within the therapeutic range in both groups. In period 2, the addition of lopinavir/ritonavir to the immunosuppressant regimen enabled a reduction in the dose of immunosuppressants required to maintain trough concentrations within the therapeutic range (to 0.3 mg/day for tacrolimus and 75 mg/day for cyclosporine). Immunosuppressant doses were not modified by the reintroduction of enfuvirtide, there being no change in the mean trough concentrations over the 3 periods. CD4 cell counts remained at about 200 cells/mm³. The HIV RNA viral load remained undetectable. Both groups displayed signs of mild cytolysis and cholestasis due to the recurrence of HCV, whereas no renal insufficiency was observed. Enfuvirtide is an attractive alternative to standard ARV therapy, facilitating the management of drug-drug interactions shortly after liver transplantation. Moreover, the lack of liver toxicity renders this drug valuable in the event of a severe HCV recurrence.

Predictors of complication after percutaneous ultrasound-guided kidney biopsy in HIV-infected individuals: Possible role of hepatitis C and HIV co-infection. Tabatabai S, Sperati CJ, Atta MG, et al. *J Am Soc Nephrol.* 2009 Oct 1. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/19808221?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_RESULTSPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

BACKGROUND AND OBJECTIVES: HIV-infected patients often undergo kidney biopsy. The risks of percutaneous ultrasound-guided kidney biopsy in this population are not well established. **DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS:** This was a case-control, single-center study of 1116 (243 with HIV infection and 873 without) consecutive ultrasound-guided biopsies from 1024 patients. The primary outcome was any major or minor complication. Major complications included biopsy-associated bleeding that required transfusion, angiography, or surgery; hypotension that required intervention; and death. Minor complications included development of a hematoma or gross hematuria. The odds of complication was assessed with logistic regression. **RESULTS:** Overall complication rates (8.6 versus 7.2%) did not significantly differ between HIV-infected and noninfected individuals. HIV-positive status did not predict complication. In the entire cohort, hepatitis C infection was associated with a 2.08 (95% confidence interval [CI] 1.47 to 2.93) increased odds of complication, and each 10,000-cells/mm³ decrease in prebiopsy platelet count a 1.05 (95% CI 1.02 to 1.08) increased odds of complication. In addition, prebiopsy hematocrit <30% and estimated GFR <30 ml/min per 1.73 m² were associated with major complication. Whereas the association of prebiopsy platelet count was not modified by HIV infection, hepatitis C/HIV co-infection was associated with a 5.71 (95% CI 1.89 to 17.2) increased odds of complication as compared with 1.27 (95% CI 0.73 to 2.19) in hepatitis C-positive/HIV-negative individuals. **CONCLUSIONS:** Ultrasound-guided percutaneous kidney biopsy is a relatively safe, well-tolerated procedure in the HIV-infected population. HIV-infected individuals who are co-infected with hepatitis C seem to be at greatest risk.

Hepatitis C viral kinetics during treatment with Peg IFN-alpha-2b in HIV/HCV coinfecting patients as a function of baseline CD4+ T-cell counts. Avidan NU, Goldstein D, Rozenberg L, et al. *J Acquir Immune Defic Syndr.* 2009 Sep 30. [Epub ahead of print]

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

BACKGROUND: HIV/hepatitis C virus (HCV) coinfecting patients are known to have lower sustained viral response (SVR) rates than HCV monoinfected patients. However, the role of CD4 T-cell counts on viral kinetics and outcome is not fully understood. **METHODS:** HCV RNA kinetics (bDNA v3, lower limit of detection (LD) = 615 IU/mL) was analyzed in 32 HIV/HCV coinfecting persons treated with Pegylated-interferon-alpha2b (1.5 mug/kg weekly) and ribavirin (1-1.2 g daily) for 48 weeks and compared with **RESULTS** obtained from 12 HCV monoinfected patients treated with the same regimen. **RESULTS:** Baseline CD4 T-cell counts \geq 450 cells/mm³ were significantly ($P < 0.002$) associated with SVR in coinfecting genotype 1 patients. First phase decline was significantly lower among patients with low as compared with high CD4 counts ($P < 0.03$) and among coinfecting compared with monoinfected patients ($P < 0.002$). Second phase decline slope showed a similar trend for coinfecting patients. **CONCLUSIONS:** Low baseline CD4 T-cell count is associated with slower HCV viral kinetics and worse response to treatment among HIV coinfecting patients, suggesting HCV treatment response depends on immune status. HCV genotype 1 coinfecting patients have slower first phase viral kinetics than HCV monoinfected patients. First phase viral decline (>1.0 log) and second phase viral decline slope (>0.3 log/wk) are excellent predictors of SVR for coinfecting patients.

Acute hepatitis C in HIV-infected patients: rare spontaneous clearance correlates with weak memory CD4 T-cell responses to hepatitis C virus. Schnuriger A, Dominguez S, Guiguet M, et al. *AIDS*. 2009 Oct 23;23(16):2079-89.

http://www.ncbi.nlm.nih.gov/pubmed/19710595?itool=EntrezSystem2.PEntrez.Pubmed.PubmedRESULTSPanel.Pubmed_RVDocSum&ordinalpos=2

OBJECTIVES: To explore the parameters of specific immunity to hepatitis C virus (HCV) associated with virus clearance during acute HCV infection in HIV coinfection. **METHODS:** HIV-infected patients without prior HCV infection were prospectively enrolled for acute hepatitis C and followed up over 15 months. HCV-specific T cells were assessed by proliferation, ELISpot, intracellular cytokine staining and pentamer assays. Pegylated-interferon-alpha and ribavirin were proposed if HCV persisted at M3. **RESULTS:** Thirty eight acutely HCV-infected HIV-positive patients were enrolled. HCV genotypes were predominantly 4 and 1. Five patients (13%) showed spontaneous clearance and 20 initiated treatment, of whom 13 (65%) showed sustained virologic responses. Before M3, HCV-specific proliferative responses observed in 35% cases, were associated with lower HCV viral load ($P = 0.04$) and predictive of spontaneous clearance ($P = 0.02$), particularly anti-NS4 responses ($P = 0.03$). These HCV-specific proliferative responses were associated with HIV-p24-specific responses ($P = 0.002$) independently from the HIV stage. Interferon-gamma-producing T cells specific for HCV were detectable ex vivo in 81% cases but at low intensity (<150 spot forming cells/10 peripheral blood mononuclear cells) and were independent of the HCV outcome. Low frequencies of pentamer-positive HCV-specific CD8 cells (0.01-0.05%) detected in nine of 12 patients were mainly effector-memory PD-1-negative T cells. Twelve days of HCV-specific in-vitro culture induced amplification of CD4 T cells coproducing interleukin-2 and interferon-gamma but rarely of CD8 T cells. **CONCLUSION:** Acute HCV infection in HIV-coinfected patients is characterized by a low rate of spontaneous clearance and weak HCV-specific memory T cells, not strictly related to HIV-induced immune defects, and which correlate with virus clearance.

EPIDEMIOLOGY, DIAGNOSTICS, AND MISCELLANEOUS WORKS

The hepatitis C virus and its hepatic environment: a toxic but finely tuned partnership.

Perrault M, Pêcheur EI. *Biochem J*. 2009 Oct 12;423(3):303-14.

http://www.ncbi.nlm.nih.gov/pubmed/19807698?itool=EntrezSystem2.PEntrez.Pubmed.PubmedRESULTSPanel.Pubmed_RVDocSum&ordinalpos=1

Twenty years after its discovery, HCV (hepatitis C virus) still infects 170 million people worldwide and cannot be properly treated due to the lack of efficient medication. Its life cycle must be better understood to develop targeted pharmacological arsenals. HCV is an enveloped virus bearing two surface glycoproteins, E1 and E2. It only infects humans through blood transmission, and hepatocytes are its only target cells. Hepatic trabeculae are formed by hepatocyte rows surrounded by sinusoid capillaries, irrigating hepatic cells. Hepatocytes are polarized and have basolateral and apical poles, separated by tight junctions in contact with blood and bile respectively. In blood, HCV remains in contact with lipoproteins. It then navigates through hepatic microenvironment and extracellular matrix, composed of glycosaminoglycans and proteins. HCV then encounters the hepatocyte basolateral membrane, where it interacts with its entry factors: the low-density lipoprotein receptor, CD81 tetraspanin, and the high-density lipoprotein (scavenger) receptor SR-BI (scavenger receptor BI). How these molecules interact with HCV remains unclear; however, a tentative sequence of events has been proposed. Two essential factors of HCV entry are the tight junction proteins claudin-1 and occludin. Cell polarity therefore seems to be a key for HCV entry. This raises several exciting questions on the HCV internalization pathway. Clathrin-dependent endocytosis is probably the route of HCV transport to intracellular compartments, and the ultimate step of its entry is fusion, which probably takes place within endosomes. The mechanisms of HCV

membrane fusion are still unclear, notably the nature of the fusion proteins is unknown and the contribution of HCV-associated lipoproteins to this event is currently under investigation.

Serum cystatin C level is a good prognostic marker in patients with cirrhotic ascites and normal serum creatinine levels. Seo YS, Jung ES, An H, et al. *Liver Int.* 2009 Nov;29(10):1521-7. Epub 2009 Sep 2.

http://www.ncbi.nlm.nih.gov/pubmed/19725889?itool=EntrezSystem2.PEntrez.Pubmed.PubmedRESULTSPanel.Pubmed_RVDocSum&ordinalpos=6

BACKGROUND/AIMS: Serum creatinine (Cr) is not a reliable marker for early detection of renal dysfunction in patients with cirrhotic ascites. Several reports have suggested that cystatin C (CysC) is more sensitive than Cr for detecting reduced renal function in these patients. This study evaluated the clinical significance of CysC in patients with cirrhotic ascites and a normal serum Cr level.

METHODS: We enrolled patients with ascites and a normal serum Cr level (<1.2 mg/dl). Liver function tests, international normalized ratio (INR) and serum Cr and CysC levels were measured on the same day for all patients. CysC levels were measured using the automated latex-enhanced immunonephelometric method. The endpoint of follow-up was the development of hepatorenal syndrome (HRS) or mortality. **RESULTS:** Seventy-eight patients with cirrhotic ascites were enrolled in the study (58 men and 30 women; age, 53+/-11 years). The underlying liver diseases in these patients were chronic hepatitis B (37%), chronic hepatitis C (4%), alcoholic liver disease (53%) and others (6%). Forty-six (59%) and 32 (41%) patients were in Child-Pugh classes B and C respectively. HRS developed in 14 patients during the follow-up period (349+/-241 days), with cumulative incidences of 10.2% and 20.4% at 6 and 12 months respectively. The CysC level was the only independent predictive factor for HRS. Twenty-three patients died during the follow-up period. CysC level and INR were independent factors for predicting mortality. **CONCLUSION:** Serum CysC level is a good marker for predicting HRS and survival in patients with cirrhotic ascites and a normal Cr level.

Self reported health status, and health service contact, of illicit drug users aged 50 and over: a qualitative interview study in Merseyside, United Kingdom. Beynon CM, Roe B, Duffy P, Pickering L. *BMC Geriatr.* 2009 Oct 9;9:45.

http://www.ncbi.nlm.nih.gov/pubmed/19818114?itool=EntrezSystem2.PEntrez.Pubmed.PubmedRESULTSPanel.Pubmed_RVDocSum&ordinalpos=1

BACKGROUND: The populations of industrialised countries are ageing; as this occurs, those who continue to use alcohol and illicit drugs age also. While alcohol use among older people is well documented, use of illicit drugs continues to be perceived as behaviour of young people and is a neglected area of research. This is the first published qualitative research on the experiences of older drug users in the United Kingdom. **METHODS:** Semi-structured interviews were conducted in Merseyside, in 2008, with drug users aged 50 and over recruited through drug treatment services. Interviews were recorded and transcribed and analysed thematically. Only health status and health service contact are reported here. **RESULTS:** Nine men and one woman were interviewed (age range: 54 to 61 years); all but one had been using drugs continuously or intermittently for at least 30 years. Interviewees exhibited high levels of physical and mental morbidity; hepatitis C was particularly prevalent. Injecting-related damage to arm veins resulted in interviewees switching to riskier injecting practices. Poor mental health was evident and interviewees described their lives as depressing. The death of drug-using friends was a common theme and social isolation was apparent. Interviewees also described a deterioration of memory. Generic healthcare was not always perceived as optimal, while issues relating to drug specific services were similar to those arising among younger cohorts of drug users, for example, complaints about inadequate doses of prescribed medication. **CONCLUSION:** The concurrent effects of drug use and ageing are not well understood but are thought to exacerbate, or accelerate the onset of, medical conditions which are more prevalent in

older age. Here, interviewees had poor physical and mental health but low expectations of health services. Older drug users who are not in contact with services are likely to have greater unmet needs. The number of drug users aged 50 and over is increasing in Europe and America; this group represent a vulnerable, and in Europe, a largely hidden population. Further work to evaluate the impact of this change in demography is urgently needed.

Personalized medicine: Factors influencing reimbursement. Meckley LM, Neumann PJ. Health Policy. 2009 Oct 6. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19815307?itool=EntrezSystem2.PEntrez.Pubmed.PubmedRESULTSPanel.Pubmed_RVDocSum&ordinalpos=1

OBJECTIVES: Personalized medicine (PM) has attracted tremendous interest, but yielded few marketed products. We examined factors influencing the reimbursement of existing PM technologies. **METHODS:** We conducted six case studies of the following paired genetic tests and treatments: HER2/neu with trastuzumab (Herceptin); hepatitis C genotyping with ribavirin/pegylated interferon; Oncotype DX with chemotherapy; UGT1A1 with irinotecan (Camptosar); VKORC1/CYP2C9 with warfarin; BRCA1/2 with prophylactic surgical measures; and Oncotype DX with chemotherapy. We developed a framework for categorizing PM technology, and assessed factors influencing reimbursement, including quality of evidence, type of regulatory oversight, presence of clinical guidelines, and cost-effectiveness. **RESULTS:** PM is not a monolithic concept, but rather encompasses different types of technology. The strength of evidence available for existing PM technology varies widely and, along with endorsement of clinical guidelines, appears to be the strongest predictor of reimbursement. In the absence of reimbursement, direct-to-consumer marketing has continued for some PM technology. The type of regulatory oversight and the **RESULTS** of cost-effectiveness analysis do not appear to be associated with reimbursement to date. **CONCLUSIONS:** To date, the promise and hype of PM has outpaced its evidentiary support. In order to achieve favorable coverage and reimbursement and to support premium prices for PM, manufacturers will need to bring better clinical evidence to the marketplace and better establish the value of their products.

Estimating population attributable risk for hepatitis C seroconversion in injecting drug users in Australia: implications for prevention policy and planning. Wand H, Spiegelman D, Law M, Jalaludin B, Kaldor J, Maher L. Addiction. 2009 Oct 5. [Epub ahead of print]

OBJECTIVE: To determine risk factors and estimate their population-level contribution to hepatitis C virus (HCV) burden. **METHODS:** Established and potentially modifiable risk factors were estimated using partial population attributable risk (PAR(p)) in a cohort of new injecting drug users (IDUs) in Sydney, Australia. **RESULTS** A total of 204 hepatitis C seronegative IDUs were recruited through street-based outreach, methadone clinics and needle and syringe programmes (NSPs) and followed-up at 3-6-monthly intervals. A total of 61 HCV seroconversions were observed during the follow-up [overall incidence rate of 45.8 per 100 person-years (95% confidence interval: 35.6-58.8)]. Overall, five potentially modifiable risk factors (sharing needles/syringes, sharing other injecting equipment, assisted injecting, frequency of injection and not being in drug treatment) accounted for approximately 50% of HCV cases observed. **CONCLUSION:** While sharing needles/syringes or other injecting equipment were associated most strongly with increased risk of HCV infection, the PAR(p) associated with these behaviours was relatively modest (12%) because they are relatively low-prevalence behaviours. Our analyses suggest that more HCV infection could be avoided by changing more common, but less strongly associated behaviours such as assisted injecting or daily injecting. **RESULTS** suggest that to have a very substantial effect on HCV, a range of risk factors need modifying. The most efficient use of scarce resources in reducing HCV infections will require complex balancing between the PAR for a given risk factor(s), the efficacy of interventions to actually modify the risk factor, and the cost of these interventions.

Health-related quality of life in dialysis patients with HCV infection. Fabrizi F, Messa P, Martin P. *Int J Artif Organs*. 2009 Oct 21. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/19844890?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_RESULTSPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Measuring the impact of chronic kidney disease (CKD) treatment on patient quality of life has become increasingly recognized as an important outcome measure. Despite improvements in the treatment of chronic kidney disease, health-related quality of life (HRQOL) is lower than in the general population. HRQOL measures, particularly the Physical Component Summary (PCS), have predictive validity for risk of both mortality and hospitalization in dialysis populations. For every 10-point lower PCS score, the relative risk (RR) of death increases by 29% (RR=1.29; 95% CI=1.23 to 1.35; $p<0.001$) and the risk of hospitalization increases by 15% (RR=1.15; 95% CI=1.11 to 1.19, $p<0.001$), according to the Dialysis Outcomes and Practice Patterns Study (DOPPS). Hepatitis C virus (HCV) infection remains prevalent among dialysis patients with a recent meta-analysis showing that anti-HCV seropositive status was an independent and significant risk factor for death in patients on maintenance dialysis. Seven studies with 11,589 unique patients on maintenance dialysis were identified; the summary estimate for adjusted relative risk (aRR) (all-cause mortality) was 1.34 with a 95% confidence interval (CI) of 1.13-1.59. In non-uremic populations HCV diminishes HRQOL, and individuals with HCV scored lower than controls across all scales of the short form 36 (SF-36). Patients achieving sustained virological responses (SVR) scored higher across all scales versus patients without SVR, especially in the physical health domains. Whether the adverse influence of HCV on survival in dialysis population is related to the negative impact of HCV on HRQOL requires further research. Information on HRQOL indices in patients with HCV on maintenance dialysis is extremely limited but the available evidence shows that HCV infection impairs HRQOL, especially in mental aspects, among patients on maintenance hemodialysis.

A seven-gene signature (cirrhosis risk score) predicts liver fibrosis progression in patients with initially mild chronic hepatitis C. Marcolongo M, Young B, Dal Pero F, et al. *Hepatology*. 2009 Oct;50(4):1038-44.

http://www.ncbi.nlm.nih.gov/pubmed/19676127?itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_RESULTSPanel.Pubmed_RVDocSum&ordinalpos=2

Fibrosis progression is the main determinant of liver disease outcome in chronic hepatitis C, being influenced by environmental and host factors. Recently, a cirrhosis risk score (CRS) based on seven single-nucleotide polymorphisms was proposed as genetic predictor of cirrhosis in hepatitis C. To assess the role of CRS in predicting fibrosis progression in patients with initially no or minimal to moderate fibrosis, we investigated 271 untreated patients with chronic hepatitis C having initial liver biopsy showing METAVIR stage F0 (n = 104), F1 (n = 101), or F2 (n = 59) who had been followed up without antiviral therapies for at least 60 months (mean 108.5 +/- 71.5 months) and had a liver biopsy at the end of this observation period. Of these, 24.4% showed no histologic progression, 75.6% progressed by at least one stage, 45.0% progressed by at least two stages, and 10.3% progressed by more than two stages. The mean CRS was significantly higher ($P = 0.005$) in patients with fibrosis progression compared with those without progression, and this difference was particularly evident ($P = 0.002$) with F0 on initial biopsy. Mean CRS scores were not associated with degree of fibrosis progression. The relative risk of fibrosis progression increased with increasing CRS values. This association was significant in males but not in females and was most evident in males with F0 at initial biopsy (odds ratio 16.5, 95% confidence interval 1.6-166; $P = 0.02$) in the presence of high CRS. Multivariate analysis confirmed the significant association of CRS score with fibrosis progression. The predictive value of CRS was confirmed in hepatitis C virus patients admitting significant alcohol intake. **CONCLUSION:** Host genetics defined by CRS predict

fibrosis progression in males with initially mild chronic hepatitis C and may become a useful parameter for prognostic evaluation and treatment decision.

BEST OF AASLD 2009

SILEN - C1: Early antiviral activity and safety of BI 201335 combined with peginterferon alfa - 2a and ribavirin in treatment - nave patients with chronic genotype 1 HCV infection.

M.S.Sulkowski¹; P.Ferenci²; C.Emanoil³; et al. Program Number: LB3

BACKGROUND: BI 201335 is a potent HCV NS3/4A protease inhibitor given once daily (QD). BI 201335 is being studied in chronic HCV genotype-1 (GT1) infection for 24 weeks in combination with pegylated interferon + ribavirin (PegIFN/RBV) in large phase II trials.

METHODS: In a double-blind, randomized, placebo-controlled, parallel group design, HCV GT1 treatment-naïve (TN) patients (pts) were randomized 1:2:2:1 to (1) placebo, (2) 240 mg BI 201335, (3) 240 mg BI 201335 with a 3 day lead-in phase (LI) of PegIFN/RBV, and (4) 120 mg BI 201335 with a 3 day LI. In each group, treatment is for 24 weeks (wks) with a background of PegIFN (180 mcg/wk) and RBV (1000/1200mg/d) for 24 or 48 wks. VL was measured by Roche TaqMan (LLOD 10 IU/ml, LLOQ 25 IU/ml). VL rebound is defined as an increase 1 log from nadir or confirmed increase 100 IU/ml if previously undetectable. **RESULTS** after 12 weeks of therapy are reported in this protocol-defined interim analysis. **RESULTS:** 232 males and 195 females were entered. Mean age=45.6 + 10.5 years, BMI=26.0 + 4.7 kg/m²; mean LOG₁₀ VL (IU/mL) at baseline=6.4. BI 201335 with PegIFN/RBV demonstrated rapid, potent antiviral activity with virologic responses at weeks 4 and 12 (see table). Mean ALT/AST improved with treatment in all groups. 16 pts reported drug-related SAEs. 18 (5.0%) pts discontinued BI 201335 due to (S)AE of which 1.7% were due to rash. Jaundice was seen in 15.9% of pts in the BI 201335 groups versus 1.4% receiving placebo. As reported previously, BI 201335 leads to a dose-dependent unconjugated hyperbilirubinemia with levels reaching a plateau in 2-4 weeks. Median (range) total bilirubin change was +1.0 (0.1-8.0), +1.5 (0.1-9.1), and +0.6 (0.2-3.9) mg/dl for BI 201335 groups 2, 3 and 4, respectively, at week 4. Other AEs were mostly mild to moderate and typical of PegIFN/RBV. Rash was observed more frequently with BI 201335. Severe rashes occurred in 2.5% and 1.4% of pts treated with BI 201335 and placebo, respectively. Changes in hematology parameters typical of PegIFN/RBV were observed in a similar pattern in all groups. **CONCLUSIONS:** SILEN-C1 confirmed robust antiviral activity with good tolerability and safety of BI 201335 given once daily in combination with PegIFN/RBV in treatment-naïve patients with chronic HCV GT-1 infection.

Once Daily Narlaprevir (SCH 900518) in Combination with PEGINTRON (Peginterferon alfa - 2b) /Ribavirin for Treatment - Nave Subjects with Genotype - 1 CHC: Interim

RESULTS from NEXT - 1, a Phase 2a Study. J.M.Vierling¹; F.Poordad²; E.Lawitz³; et al.

Program Number: LB4

BACKGROUND: Narlaprevir (NVR) is a HCV NS3 protease inhibitor that can be dosed once daily when used in combination with low dose ritonavir (RTV). NEXT-1 is being conducted to identify the optimal treatment regimen of NVR combination therapy [(NVR/RTV)/PEGINTRON (PEG)/ribavirin (RBV)]. **METHODS:** Response guided treatment of 12 weeks of NVR (200 mg QD or 400 mg QD) with RTV (100 mg QD), PEG (1.5 mcg/kg/QW), and weight based RBV (600-1400 mg/day) with or without a 4 week lead-in of PEG/RBV, or 12 weeks of NVR (100 mg BID) with RTV (100 mg BID) and PEG/RBV, all followed by an additional 12 or 36 weeks of PEG/RBV based on response at Treatment Week 4 of NVR/RTV, are being compared to PEG/RBV for 48 weeks. The primary endpoint is RVR, undetectable HCV-RNA [Roche Cobas Taqman; LLD=9.3 IU/mL] after 4 weeks of treatment with NVR/RTV. **RESULTS:** Of 111 patients treated in the US: 13% were Black, 58% male, 78% had high viral load (>600,000 IU/mL), and 61% had subtype 1a (TRUGENE). The majority of patients have been treated >8 weeks. All 12

null responders in the lead-in arms (<1 log₁₀ drop in HCV-RNA after 4 weeks of PEG/RBV) responded well to the addition of NVR/RTV; 8 achieved undetectable HCV-RNA, 3 <LLQ (25 IU/mL), and 1 <LLQ at time of discontinuation. Five subjects receiving NVR/RTV discontinued treatment due to AEs: GI-related symptoms, depression, homicidal ideation, tinnitus, and lethargy. All AEs have been observed previously with PEG/RBV therapy; no increase in rash was seen. Data on Early Virologic Response will be presented. **CONCLUSIONS:** Once daily dosing of NVR/RTV in combination with the standard of care (SOC), PEG/RBV, was highly potent in all treatment regimens, with >85% RVR in the lead-in containing regimens. Null responders to SOC lead-in had a robust anti-viral response during 4 weeks of NVR/RTV therapy. NVR/RTV was safe, well tolerated, and produced no unique AEs. Completion of NEXT-1 will define the ability of once daily NVR/RTV with SOC (PEG/RBV) to achieve high SVR rates in HCV genotype 1 patients.

Genome wide analysis of patients from the IDEAL study identifies a polymorphism upstream of the IL28B (=IFN - 3) gene that is strongly associated with SVR in patients with HCV – 1. A.J.Thompson¹; A.Muir¹; M.S.Sulkowski²; et al. Program Number: LB5

BACKGROUND/AIMS: We performed a genome wide association study on a large, well characterized genotype 1 HCV treatment cohort to identify genetic determinants of treatment outcome. **METHODS:** 1604 of 3070 patients treated with pegIFN/RBV in the IDEAL study (NEJM,2009;361:580) consented to DNA testing. To increase African American (AA) sample size, 67 patients were included from a second study comparing Caucasians and AA (NEJM,2004;350:2265). All SVR patients were included in the analysis. Non-responders were required to have received 80% pegIFN/RBV. Samples were genotyped using the Illumina Human610-quad BeadChip. After quality control, approximately 97.5% of the single nucleotide polymorphisms (SNPs) included on the chip were used in the analyses. A modified Eigenstrat method was used to control for population stratification. We searched for determinants of SVR as a primary endpoint in 3 separate populations (Caucasians, AA, Hispanics [His]) by logistic regression including other pre-treatment characteristics in the model: gender, age, BMI, ALT, viral load, steatosis score, fibrosis stage, fasting glucose and RBV dose (mg/kg/d). Bonferroni adjustment was used to correct for multiple testing. **RESULTS:** 1,137 patients were included in the final analysis. A SNP on chromosome 19 (alleles C/T) was strongly associated with SVR (P = 1.3710-28). The SNP lies 3 Kb upstream of the IL28B (IFN-3) gene. The CC genotype was associated with an approximately 2-fold increase in SVR relative to non-CC genotypes (Table 1). The CC genotype was associated with a higher rate of RVR and the majority of these patients achieved SVR. In non-RVR patients, the CC genotype was associated with a higher rate of SVR. In a regression model including baseline clinical variables, CC genotype was the strongest predictor of SVR (OR=5.2[4.1-6.7]). Differing allele frequencies in AA contributed to the lower SVR rate in this population. **CONCLUSIONS:** We have identified a SNP upstream of the IL28B (IFN-3) gene that is strongly associated with SVR rate in HCV-1 patients treated with pegIFN/RBV. IL28B genotyping has a future role in the evaluation of HCV-1 patients prior to antiviral therapy

Treatment - nave, HCV genotype 1 - infected subjects show significantly greater HCV RNA decreases when treated with 28 days of ABT - 333 plus peginterferon and ribavirin compared to peginterferon and ribavirin alone. M.Rodriguez-Torres¹; E.Lawitz²; D.Cohen³; et al. Program Number: LB6

OBJECTIVE: ABT-333 is a potent nonnucleoside HCV polymerase inhibitor with a favorable safety profile in healthy subjects. This study assesses the safety, antiviral activity, and pharmacokinetics (PK) of ABT-333 with peginterferon -2a (pegIFN) and ribavirin (RBV) in HCV-infected subjects. **METHODS:** 30 HCV genotype 1-infected, treatment-naive subjects were randomized to ABT-333 300 mg BID (N=8), 600 mg BID (N=8), 1200 mg QD (N=8), or placebo (n=6) for 28 days (2 days monotherapy plus 26 days with pegIFN 180 g/wk + RBV 1000-1200

mg/d, weight-based). Safety was monitored by adverse events (AEs) and lab results. ABT-333 PK profile was assessed on Day 1; samples were also collected Days 2, 4, 5, 10, 17, 24 and 28.

RESULTS: Subjects were primarily male (70%) and white (90%); 43% were of Latino ethnicity. At baseline, the mean (SD) age was 46.5 (9.8) yrs and the mean weight was 78.6 (13.2) kg. Treatment with ABT-333+pegIFN/RBV resulted in statistically significantly greater decreases in HCV RNA versus placebo+pegIFN/RBV (Figure). The least square mean maximum HCV RNA change from baseline was -3.7, -4.0, and -3.5 log₁₀ IU/mL for 300 mg BID, 600 mg BID, and 1200 mg QD ABT-333+pegIFN/RBV, respectively, compared to -1.4 log₁₀ IU/mL for placebo+pegIFN/RBV. Mean ABT-333 C_{max} and AUC increased with increasing doses and were comparable to healthy subjects. Based on mean trough values, addition of pegIFN/RBV did not alter ABT-333 PK. AEs were generally mild and attributed to pegIFN or RBV. Of ABT-333-associated AEs, nausea, headache, flatulence, and dermatitis were most common (N=2-3 for each AE). There were no serious AEs or discontinuations due to AEs. Lab abnormalities were similar in subjects receiving ABT-333 and placebo. **CONCLUSION:** ABT-333 was well tolerated for 28 days when dosed with pegIFN/RBV and resulted in significant decreases in HCV RNA versus pegIFN/RBV alone.

Hepatitis C virus (HCV) antibody seroconversion in a U.S. HIV - infected male clinical trials population. M.Holubar¹; L.E.Taylor¹; K.Wu²; R.et al. Program Number: LB14

PURPOSE: Outbreaks of sexually transmitted HCV infection have been reported among HIV-seropositive (HIV+) men who have sex with men (MSM) in Europe, Australia, New York and California. Whether this is occurring across the U.S. is unknown. **METHODS:** We evaluated the determinants of HCV antibody (Ab) seroconversion incidence among HIV+ male participants of the AIDS Clinical Trial Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) cohort. ALLRT is a long-term follow-up study of HIV+ persons randomized into selected U.S.-based clinical trials conducted by the ACTG. Seventeen ACTG studies performed HCV Ab testing from 1996-2002. HCV Ab testing at ALLRT entry began in 2002 with re-testing every 96 weeks added in 2006. 2,365 male subjects had an initial negative HCV Ab result. 1,830 of these had at least 1 subsequent HCV Ab test and were included in this analysis, contributing >7,000 person-years. We determined HCV seroconversion incidence from 1996-2008. To control for increased surveillance and variable Ab follow-up times after 1996, date of seroconversion was re-assigned as halfway between the date of the last negative and first positive HCV Ab. We evaluated associations with self-reported (previously, 5.3% or currently, 0.5%) injection drug use (IDU), time-varying CD4+ cell count and HIV RNA using multivariate Poisson regression. No sexual or non-IDU risk factor data was available. **RESULTS:** Of 1,830 males, 57% were White, 22% Black, 18% Hispanic, 2% Asian-Pacific Islander, 1% American Indian and 70% attended college. At the time of initial negative HCV Ab, mean age was 42 years (range 17-79, 52% >40), 94% were on highly active antiretroviral therapy (HAART) and 6% reported current or prior IDU. Participants had varying lengths of follow-up, with 47% contributing >4 years of person-time. Thirty-six seroconverted, with overall incidence of 0.51 per 100 person-years (95% CI = 0.36-0.7). Mean age at seroconversion was 46 years (range 22-69, 72% >40). Seroconversion was associated with IDU (25% of seroconverters reported IDU history versus 5% of non-seroconverters, p<0.001), while 75% (n=27) seroconverted in the absence of reported IDU (incidence 2.67 per 100 person-years in IDUs, 0.40 in non-IDUs). Seroconversion was associated with HIV RNA >400 copies/ml (44% at time of Ab-positivity vs. 21% at time of last negative Ab, p<0.001) but not with CD4+ cell count. **CONCLUSIONS:** Incident HCV infection is occurring in a U.S. HIV+ male population despite engagement in care with HAART, potentially through non-parenteral means. HCV Ab development was not related to immune status, but was associated with inadequate HIV suppression.

GI - 5005 Therapeutic Vaccine Plus Peg - IFN/Ribavirin Improves End of Treatment Response at 48 Weeks Versus Peg - IFN/Ribavirin in Naive Genotype 1 Chronic HCV Patients. J.G.McHutchison²; I.M.Jacobson³; T.D.Boyer⁴; Program Number: LB15

BACKGROUND and **AIMS:** GI-5005 is a whole heat-killed *S. cerevisiae* therapeutic vaccine expressing HCV NS3 and Core antigens. GI-5005 elicits antigen-specific T-cell responses (Hepatology 2007; 46: 816A) with the goal of improving the rate of immune-mediated elimination of HCV-infected hepatic cells. **METHODS:** Nave and non-responder (NR) chronic HCV genotype 1 patients were randomized 1:1, and stratified by prior treatment status in this open label trial; Arm 1- GI-5005 monotherapy run-in consisting of five weekly followed by 2 monthly subcutaneous (SC) doses of 40YU (1 YU = 107 yeast) GI-5005 over 12 weeks, followed by triple therapy consisting of monthly 40YU GI-5005 doses plus 48 weeks pegIFN -2a/ribavirin (SOC), Arm 2- SOC alone. NRs will receive 72 weeks of triple therapy versus SOC. **RESULTS:** Triple therapy was well tolerated with no significant new toxicities observed and an equivalent number of SOC discontinuations due to adverse events in each group; Triple therapy - 5/68 (7.3%) and SOC 5/65 (7.7%). Improvement in end of treatment response (HCV RNA < 25IU/mL by PCR assay at 48 weeks) was observed in nave genotype 1 patients in the triple therapy group compared to SOC alone (all randomized); Triple therapy - 37/53 (70%) vs SOC- 27/49 (55%), one-tailed Fisher's exact test p=0.09. Complete response (HCV RNA <25IU/mL) was assessed in NRs at week 48 (all randomized); Triple therapy - 6/19 (32%) vs SOC- 6/19 (32%). Race, baseline viral load, SOC compliance, and discontinuations did not reveal a significant influence on the observed treatment effect. **CONCLUSIONS:** Triple therapy with GI-5005 plus pegIFN/ribavirin is well tolerated and improved week 48 ETR rates compared to SOC in genotype 1 nave patients. Final sustained virologic response 24 weeks post-treatment will be reported after completion of the trial. These data support further investigation of GI-5005 triple therapy as well as novel combination strategies for GI-5005 with other HCV inhibitory agents.

Virological Response and Safety of BI 201335 protease inhibitor, Peginterferon alfa 2a and Ribavirin treatment of HCV genotype - 1 patients with compensated liver cirrhosis and non - response to previous peginterferon / ribavirin.S.Poll¹; T.Berg²; M.Bonacini³; et al. Program Number: LB16

BACKGROUND: BI 201335 is a highly potent and specific HCV NS3/4A protease inhibitor. A phase 1 trial in treatment-experienced HCV GT-1 patients demonstrated a mean viral load (VL) reduction of 5.3 LOG₁₀ (IU/mL) for BI 201335 given once daily after 28 days in combination with peginterferon alfa (PegIFN) 2a and ribavirin (RBV). We now describe a phase 1b trial which has assessed safety, short-term efficacy, and pharmacokinetics of BI 201335 in GT-1 patients with compensated liver cirrhosis and non-response to previous PegIFN/RBV, a difficult-to-treat HCV population with a high unmet medical need. **METHODS:** In this open-label, sequential group comparison, HCV GT-1 patients with compensated liver cirrhosis who have never achieved undetectable VL under previous PegIFN/RBV were treated with 240 mg once (QD; n=6) or twice daily (BID; n=7) in combination with PegIFNa2a (180 mcg/week) and RBV (1000/1200mg/d) for 28 days. All patients received a single loading dose of 480mg of BI 201335 as the first dose. Plasma HCV RNA was measured by Roche COBAS TaqMan assay. **RESULTS:** Mean age was 54 years, BMI 26 kg/m². Mean VL at baseline was 6.1 and 6.3 LOG₁₀ (IU/mL) in both groups. All patients showed a rapid and continuous decline in VL. Mean VL declines on day 28 in the 240mg QD and BID groups were -4.9 and -5.0 LOG₁₀, respectively. No breakthrough (>0.8 log rebound from VL nadir) was observed during treatment. At day 28, 5/6 and 5/7 patients achieved VL below level of quantification (< 25 IU/ml) in the QD and BID group. Furthermore, 4/6 and 1/7 patients had VL below level of detection (<10 IU/ml) in the 240mg QD and BID groups. There were no SAE in the 240mg QD group and 2 SAE in the 240mg BID group. Both were cases of mild to moderate hepatic decompensation attributed to PegIFN/RBV by the investigators. Two patients in the BID

group discontinued treatment early, one due to nausea, one due to hepatic decompensation (SAE). Jaundice due to isolated unconjugated hyperbilirubinemia was reported in 2/6 and 1/7 patients at 240mg QD and BID, respectively. Other AE were mainly mild to moderate and typical of PegIFN/RBV. Lab analyses showed decreases of ALT / AST as well as blood cell counts typical of PegIFN/RBV. **CONCLUSIONS:** BI 201335 once or twice daily combined with PegIFN/RBV exhibited potent antiviral activity in non-responder patients with liver cirrhosis. BI 201335 also exhibited a good safety and tolerability profile in these patients, allowing for their inclusion into the ongoing phase 2 program. These data also confirm that IFN non-responsiveness in previous non-responders can be overcome by rapid and profound inhibition of viral replication by BI 201335.

The Beneficial Effect of Vitamin D with Combined Peg Interferon and Ribavirin for Chronic HCV Infection. S.M.Abu-Mouch^{1,3}; Z.Fireman²; J.Jarchovsky³; N.Assy. Program Number: LB20

BACKGROUND: The combination therapy of pegylated-interferon-alpha2 and ribavirin is considered the standard of care for chronic hepatitis C (HCV). A sustained viral response (SVR) is obtained in 40-50% of naive patients with genotype 1. Vitamin D is a potent immunomodulator whose impact on virologic response rates of interferon-based treatment of chronic HCV is unknown. **AIM:** To assess whether the addition of vitamin D to the conventional bi-therapy could improve treatment efficacy. **METHODS:** Fifty-eight patients with confirmed chronic HCV were randomized into two groups (intent-to-treat population): 27 (treatment group, mean age 47.1 years, body mass index [BMI] 27.4, 50% male) received pegylated-interferon-alpha2b (1.5 g/kg once weekly) plus ribavirin (1000-1200 mg/daily) together with vitamin D (1000-4000 IU/daily, serum level >32 ng/ml), and 31 (controls, mean age 49.7 years, BMI 24.3, 60% male) received the same therapy without vitamin D. HCV RNA was assessed by RT-PCR (sensitivity, 50 IU/ml). Undetectable HCV RNA at week 12 (considered as complete EVR.) **RESULTS:** Demographics, disease characteristics, ethnicity, baseline biochemical parameters and adherence to treatment were similar in both groups. The treatment group had a higher mean BMI (27.4 vs 24.3; P<0.01), viral load (68% vs 58%, P<0.01), and fibrosis (Metavir scores >F2: 55% vs 18%, P<0.001) than the controls. All but one treated patient (96%) and 48% (15/31) controls were HCV-RNA negative at week 12 (P<0.001). There were no adverse events during therapy. **CONCLUSIONS:** This preliminary study confirms the benefit of adding vitamin D to conventional bi-therapy in the treatment of chronic HCV.

Week 8 is the optimal time point to select patients with chronic hepatitis C, genotype 1/4 for treatment extension to 72 weeks. T.Scherzer¹; H.Kerschner²; S.Beinhardt¹; et al. Program Number: 34

BACKGROUND: In patients with chronic hepatitis C duration of treatment can be individualized based on the rapidity of HCV elimination from blood. The optimal time point to select patients for treatment extension is not well established. To determine which patients would benefit most from extended treatment, SVR and relapse rates were determined according to viral load at week (wk) 8 and 12 of treatment in patients who participated in two prospective randomized trials in Austria. **METHODS:** The impact of the time of HCV elimination at weeks (wks) 4, 8 and 12 on treatment outcome was analyzed in 317 HCV GT1/4 pts (age 44.0±10.2yrs, BMI 25.5±4.1, male: n= 207, female: n= 110; GT1: n=295, GT4: n=22) participating in 2 randomized studies. HCV-RNA was measured by COBAS AmpliCor HCV Test (Roche Molecular Systems, Branchburg, NJ; limit of detection 50 IU/mL). All patients were treated with 180g peginterferon2a/wk plus 1000-1200 mg ribavirin/day. In one study all patients were treated for 48 wks (Ferenci P et al, J Hepatol 2006), in the other for 24, 48, or 72 wks, depending on the rapidity of viral clearance (Ferenci P et al, Gastroenterology 2008). **RESULTS:** In pts with RVR SVR (TPP) rates were 93.6% (44/47) and 96% (24/25) treated for 24 wks or 48 wks, respectively. Of patients who became HCV RNA negative at wk 8 92.8%

(64/69, treated for 48 wks) and 100% (13/13, treated for 72 wks) had a SVR. In contrast, of the patients with detectable HCV-RNA at wk 8 only 55.5% (55/94, treated for 48 wks) but 81.8% (18/22; $p < 0.05$) when treated for 72 wks had a SVR. Of all patients with undetectable HCV-RNA at wk 12 84.6% (115/136) and 82.1% (23/28) had a SVR when treated for 48 or 72 wks, respectively. Partial responders had equal SVR rates in both treatment regimes (30.9% vs 36.4%), but higher relapse rates when treated for 48 wks (62.2% vs 20%) (table 1). **CONCLUSION:** Measurement of HCV-RNA at wk 8 is the optimal time to identify patients most likely to benefit from extended peginterferon alfa-2a/ribavirin combination therapy. Furthermore, shortening of therapy in patients with RVR produces the same high SVR rates than in patients treated for 48 wks.

Identifying HCV genotype 2/3 patients who could receive a 16 - week abbreviated course of peginterferon alfa - 2a (40KD) plus ribavirin. M.L.Shiffman¹; J.Bronowicki²; S.Zeuzem³; et al.
Program Number: 35

BACKGROUND: Based on the ACCELERATE trial abbreviated treatment (16 weeks) with peginterferon alfa-2a (40KD; PEGASYS) plus ribavirin (RBV) may be considered in G2/3 patients with a low baseline viral load who achieve undetectable HCV RNA (<50 IU/mL) by week 4. However, comparison of SVR rates between standard and abbreviated treatments by intention to treat analyses may be confounded by higher drop-out rates in the group who received a longer duration of therapy. **METHODS:** We performed a post-hoc analysis from the ACCELERATE study of HCV genotype 2/3 infected patients randomized to 16 or 24 weeks of peginterferon alfa-2a (40KD) (180 g/week) plus RBV (800 mg/day) who achieved an RVR and completed designated treatment. The primary efficacy endpoint was SVR (HCV RNA <50 IU/mL 24 weeks after an untreated follow-up period). **RESULTS:** Baseline characteristics of the 863 patients completing 16 or 24 weeks treatment were well matched. Rates of SVR and relapse are described in the table. MLR analysis confirmed completion of 24 weeks treatment as an independent predictor of SVR (OR 2.12, 95% CI 1.38-3.24; $p = 0.0006$) as well as lower body weight (OR 0.97, 95% CI 0.96-0.98; $p < 0.0001$) and lower baseline HCV RNA (OR 0.66, 95% CI 0.51-0.86; $p = 0.0017$). Restricting the analysis to G2/3 RVR patients with a baseline viral load <400 000 IU/mL showed similar SVR rates among patients completing 24 or 16 weeks treatment (95% vs 91% respectively; $p = 0.2012$). Among G2 patients SVR rates were 90% vs 95% and for G3 patients SVR rates were 91% vs 95%. In the combined G2/3 population SVR rates were similar (>82%) among patients receiving >80% planned dose of RBV completing 16 or 24 weeks of treatment with no relationship between % planned dose of RBV and rate of SVR. Too few patients had cumulative dose of RBV <80% to draw conclusions. **CONCLUSIONS:** Patients infected with HCV genotype 2/3 tolerating treatment with peginterferon alfa-2a plus RBV should be encouraged to complete the full 24-week treatment duration. Modest decreases in RBV dose do not compromise SVR rates. For patients with a low baseline viral load who achieve an RVR, SVR rates are similar whether patients complete 16 or 24 weeks of treatment. Abbreviated treatment may be considered in these patients.

Standard versus higher induction doses of peginterferon alfa - 2a (40KD) and/or higher ribavirin (RBV) in HCV G1 patients with high viral load and body weight 85 kg: Final RESULTS of the PROGRESS study. K.Reddy¹; M.L.Shiffman²; M.Rodriguez-Torres³; Program Number: 61

BACKGROUND: Patients infected with HCV G1 with a high viral load and high body weight achieve lower rates of SVR compared to G1 patients with lower viral load and body weight. The PROGRESS study investigated higher induction doses of peginterferon alfa-2a (PEGASYS) and/or higher RBV doses to explore the impact on rates of SVR and safety. **METHODS:** Overall 1175 G1 patients with a baseline viral load 400,000 IU/mL and body weight 85 kg were randomized (in a ratio of 1:1:2:2) to 48 wks of 180 g/wk peginterferon alfa-2a (40KD) plus RBV either at a dose of 1200 mg/day or 1400/1600 mg/day (groups A and B) or 12 wks of 360 g/wk peginterferon alfa-2a

(40KD) followed by a further 36 wks of 180 g/wk plus RBV either at a dose of 1200 mg/day or 1400/1600 mg/day (groups C and D). For arms B and D, RBV was given at 1400 mg for patients 85 to <95kg and at 1600 mg for 95kg. The primary efficacy endpoint was SVR (% of patients with HCV RNA <15 IU/mL) 24 wks after untreated follow-up. **RESULTS:** Baseline characteristics and treatment outcome are described in the table. The odds ratio (95% CI; p-value) of SVR among groups C+D versus A+B was 1.075 (0.831-1.391; p=0.584) and the odds for SVR among groups B+D versus A+C was 1.004 (0.788-1.279; p=0.974). **CONCLUSIONS:** In these difficult to cure patients high and comparable rates of SVR were achieved across all treatment arms. Higher rates of SVR were observed among patients 95 kg and those with a NAS (non alcoholic fatty liver disease activity score) score 3 with induction dosing of peginterferon alfa-2a (40KD) and/or higher RBV doses. Higher doses of peginterferon alfa-2a (40KD) and/or RBV were well tolerated with a similar proportion of patients reporting SAEs and discontinuing peginterferon alfa-2a or RBV for safety reasons.

High Sustained Virologic Response (SVR) in Genotype 1 (G1) Null Responders to Peg - Interfeon alfa - 2b (P) plus Ribavirin (R) When Treated with Boceprevir (Boc)

Combination Therapy. P.Y.Kwo¹; E.Lawitz²; J.McCone³; et al. Program Number: 62
HCV SPRINT-1 had two arms with a 4-week lead-in of P (1.5 g/kg/QW) plus R (800-1400 mg/day) prior to the addition of Boc (800 mg TID) for an additional 24 or 44 weeks of therapy in nave G1 patients (pt). This design allowed the determination of viral response based on precisely defined P/R response. Data from IDEAL demonstrating that a 1 log₁₀ decrease in viral load at W4 corresponded to a ~2 log₁₀ decrease at W12, permitted definition of a 'null' response to P/R therapy (<1 log₁₀@W4). Viral response was assessed by Roche Taq-Man (LLD=15 IU/ml) at multiple times including 24-week post-treatment (SVR). **RESULTS:** Pts were all G1 (1a>1b) with 15% Black, 7% cirrhotics and 90% high viral load. W4 virology was available for 96 and 101 patients in the 28W and 48W arms, respectively. Combining these 2 arms 60% of null responders (30/50) had undetectable HCV-RNA at W24, including 56% (9/16) of those with the poorest W4 response (<0.5 log drop). SVR was 55% (12/22) and 25% (7/28) in the 48W and 28W arms respectively, with 44% (4/9) of the worst responders achieving SVR after 48 weeks of Tx. SVR for the 'non-null' responders was 81% and 72% for 48W and 28W arms. Multivariate regression showed W4 response to be a predictor of W24 response (All) and SVR (48W Tx; OR=8.2, p<0.005). We could not define a minimal P/R response at W4 that reliably predicted poor viral response. In >95% of pts, addition of Boc for 4 weeks led to a >1.5 log decline in viral load, and only those who never became undetectable had a poor SVR. **CONCLUSION:** Null responders to P/R (lead-in) therapy had a high SVR after 44 additional weeks of Boc plus PR therapy. Response is higher in 'non-null' patients, but no factors could clearly define a group of patients who do not achieve SVR. Since null responders to P/R responded well to the addition of Boc, and benefited from longer Boc/P/R therapy, the ability to treat these pts for up to 44 weeks with all 3 drugs is likely an important therapeutic advantage.

Efficacy and Safety of albinterferon alfa - 2b in Combination with ribavirin in Treatment Nave Patients with chronic hepatitis C genotype 1. M.S.Sulkowski; S.Zeuzem; et al. Program Number: 64

BACKGROUND: A phase 3, randomized, active-controlled, multi-center study evaluated the efficacy and safety of albinterferon alfa-2b (albIFN), a genetic fusion polypeptide of albumin and interferon alfa-2b in chronic HCV-1 patients. **METHODS:** In total, 1331 patients were randomized 1:1:1 to one of the 3 treatment groups: albIFN 900 g q2wk; albIFN 1200 g q2wk (dose reduced to 900 g); PEG-IFN2a 180 g q1wk for 48 wks, in combination with weight-based ribavirin 1000-1200 mg/day. Randomization was stratified by baseline HCV RNA levels (or < 800,000 IU/mL), BMI (or < 25 kg/m²) and race (Black/African-American or other). The primary endpoint was sustained

virologic response SVR, (defined as serum HCV RNA < 15 IU/mL at wk 72). **RESULTS:** The study achieved the primary objective of demonstrating non-inferiority of albIFN 900 g (p=0.0008) and albIFN 1200 g (p=0.0029) versus PEG-IFN2a for SVR. In the intention-to-treat population, SVR rates were 51.0% (225/441), 48.2% (213/442), and 47.3% (208/440) in the PEG-IFN2a, albIFN 900 and albIFN 1200 groups, respectively. Multivariate analysis identified the following predictors of SVR: HCV RNA <400,000 IU/mL, age <45, normal GGT, high ALT, F0-2 fibrosis, and race (non-black), consistent with previous studies. Early antiviral response had a high positive predictive value (PPV) for SVR in all treatment groups. The PPV of initial virologic response at Week 2 (IVR; >2 log viral decline or HCV RNA < LOQ) was 73-84%; the PPV of rapid virologic response at Week 4 (RVR; HCV RNA<LOQ) was 83-88%. In PEG-IFN2a, albIFN 900 and albIFN 1200 groups, the rates of IVR were 30.2%, 33.9%, and 38.2%; the rates of RVR were 26.5%, 24.0%, and 28.9%, respectively. Safety analyses showed: 1) Rates of serious and/or severe adverse events (AE) were 23.1%, 24.0% and 28.2%; 2) Treatment discontinuations due to AEs were 4.1%, 10.4% and 10.0%; 3) Severe or serious pulmonary events were rare and blinded central review of chest x-rays during treatment showed comparable rates of interstitial lung findings: 4.2%, 2.4% and 4.5%. The rates of hematologic abnormalities were similar in albIFN 900 versus PEG-IFN2a. **CONCLUSIONS:** Albinterferon alfa-2b 900g administered q2wk demonstrated comparable efficacy to PEG-IFN2a in patients with chronic HCV-1. The overall incidence of serious or severe adverse events was similar between these two treatments.

PROVE3 Final RESULTS and 1 - Year Durability of SVR with Telaprevir - Based Regimen in Hepatitis C Genotype 1 - Infected Patients with Prior Non - response, Viral Breakthrough or Relapse to Peginterferon - Alfa - 2a/b and Ribavirin Therapy. J.G.McHutchison¹; M.P.Manns²; A.Muir¹; Program Number: 66

BACKGROUND: PROVE3 is a randomized Phase 2 study assessing safety and efficacy of telaprevir (T) plus Peginterferon-alfa-2a (P) Ribavirin (R) in HCV genotype 1 pts who failed prior PR treatment. **METHODS:** Randomization was 1:1:1:1 to: T/PR for 12-wks, then PR for 12-wks (T12/PR24); T/PR for 24-wks, then PR for 24-wks (T24/PR48); T/P for 24-wks (T24/P24); or placebo/PR (P 180 g/wk, R 1000-1200 mg/day) for 24-wks, then PR for 24-wks (PR48). Treatment was discontinued if a protocol-defined stopping rule was met. HCV RNA was assessed 48-wks after treatment only in pts in T arms who completed treatment and achieved SVR. **RESULTS:** Of 453 pts included in ITT analysis, 418 (92%) had baseline HCV RNA 800,000 IU/mL, (267) 59% had genotype 1a, 196 (43%) had cirrhosis or bridging fibrosis and 40 (9%) were black; 235 (52%) completed assigned treatment. Discontinuation due to protocol-defined stopping rules were 15% in T12/PR24, 23% in T24/PR48, 37% in T12/P24, and 59% in PR48. 10%, 25%, 9% and 4% of pts discontinued due to AEs in T12/PR24, T24/PR48, T24/P24, and PR48, respectively. Viral breakthrough rates were 11%, 10%, 21%, and 3% in T12/PR24, T24/PR48, T24/P24, and PR48, respectively. Relapse rates were 28%, 4%, 53% and 52% in T12/PR24, T24/PR48, T24/P24, and PR48, respectively, 24-wks after treatment. In the T regimens, no late relapses occurred 48-wks after treatment. AEs occurring with a greater incidence in T12/PR24 or T24/PR48 than PR48 included fatigue, nausea, headache, rash, pruritus, diarrhea, anemia, insomnia, pyrexia, alopecia, and chills. Grade 3 rash was observed in 5%, 4%, 3% and 0% of pts in T12/PR24, T24/PR48, T24/P24, and PR48, respectively. Grade 3 anemia was observed in 0%, 6%, 1% and 1% of pts in T12/PR24, T24/PR48, T24/P24 and PR48, respectively. **CONCLUSIONS:** SVR rates in all treatment groups receiving T/PR regimens were significantly higher than with PR48. Other than 1 pt lost to follow-up, all pts who completed T regimen and achieved SVR maintained virologic response 48-wks after the end of treatment. The general safety profile of these regimens was similar to that observed in treatment-naïve pts. Pts who failed prior PR therapy can successfully be treated with a T-based regimen and maintain SVR 1 year after the end of treatment.

HCV - Genotype - Specific Influences on Incident Diabetes: the Effect of Sustained Viral Response to Antiviral Therapy. M.Manos; W.Zhao; V.Shvachko. Program Number: 116

Evidence suggests HCV infection increases the risk of diabetes through viral-genotype-specific mechanisms. To assess how HCV antiviral therapy affects diabetes, we studied post treatment (any IFN/ribavirin) incident diabetes in patients treated 1999-2006 in the Northern California Kaiser Permanente Medical Care Program. We used electronic health plan records of 2,040 mono-infected patients without diabetes history prior to therapy end. Overall, 60% were men, mean age 50 years, and 47% had SVR. Most (68%) were non-Hispanic white, 7% black, 8% Asian and 15% Hispanic. Based on BMI and age, 52% were considered to have a high diabetes risk (HDR) profile. The overall incidence (per 100 person yr, [95% CI]) of diabetes was significantly lower for those with SVR: 0.97 (0.69-1.37) vs 2.48 (2.02-3.04). Diabetes incidence was most dramatically decreased with SVR in those with a HDR profile: 1.43 (0.94-2.15) vs 3.88 (3.09- 4.86). In others, the SVR effect was not significant: 0.57 (0.31-1.05) vs 1.02 (0.64-1.60). Using Cox proportional hazard models, we determined the correlates of incident diabetes by HCV genotype (GT) for 1,164 GT-1, 408 GT-2, and 326 GT-3 patients. The figure shows adjusted hazard ratios for key factors, by genotype. Age and cirrhosis history were also accounted for. HDR profile was a significant risk factor in all cases, particularly GT-2. While strongly reducing diabetes risk in GT-1 and GT-3 patients, SVR did not significantly affect risk in GT-2 cases. Blacks (vs non-Hispanic Whites) and men were at higher risk among GT-1 cases. Hispanics appeared at higher risk among GT-2 patients. Successfully treated patients had less than half the diabetes incidence of patients without SVR, suggesting that viral clearance ameliorates the risk conferred by HCV. We also found differences in SVR effect between HCV genotypes, suggesting a lesser role of GT-2 in diabetes risk.

Sustained Virologic Response is Independently Associated with Improvement in Insulin Resistance in Genotype 1, but not Genotype 2/3, Chronic HCV Patients. A.J.Thompson²; K.Patel²; H.L.Tillmann²; J. Program Number: 117

BACKGROUND: Chronic infection with hepatitis C virus (HCV) has been associated with an increased prevalence of diabetes and insulin resistance (IR). More recently a genotype-specific association between genotype 1 HCV and IR has been proposed. However, whether this is a causal relationship remains unclear. To answer this question, we investigated the association of sustained virological response (SVR) with IR in patients enrolled in the ACHIEVE 1 and ACHIEVE 2/3 trials. **METHODS:** 2255 treatment-naïve patients with chronic HCV-1 or HCV-2/3 were enrolled in two separate phase 3, active-controlled studies of albuterferon alfa-2b plus ribavirin for 48 or 24 weeks, respectively. IR was measured at weeks 0, 12, 24, 48 and at post-treatment week 12 using the homeostasis model for assessment (HOMA-IR). Clinical evaluation included age, gender, race, body mass index (BMI), HCV viral load, ALT, GGT, total cholesterol, triglycerides, and baseline liver biopsy evaluated for steatosis, METAVIR inflammatory grade and fibrosis stage by a single pathologist. We considered IR categorically, setting a threshold of HOMA-IR > 3 (Moucari, Gastroenterology, 2008). In addition, we considered change in HOMA-IR post-therapy as a continuous variable. HOMA-IR data were log-transformed for analysis as a continuous variable. ACHIEVE 1 and ACHIEVE 2/3 cohorts were analyzed separately. **RESULTS:** Matched pre and 12-week post HOMA-IR measurements were available from 1038 non-diabetic patients (HCV-1=497, HCV-2/3=541). The SVR rate was 60% and 84% in the HCV-1 and HCV-2/3 patients, respectively. Baseline mean HOMA-IR scores were higher in patients infected with HCV-1 than HCV-2/3 (3.4 and 2.9, respectively). SVR was associated with a reduction in prevalence of IR in HCV-1, but not HCV-2/3 patients (Table 1). SVR was also associated with a reduction in mean HOMA-IR in HCV-1, but not HCV-2/3 patients (Table 1). This was independent of change in BMI, ALT, GGT and lipid levels. HOMA-IR did not change in non-responders (NR). No association of SVR with IR was seen when HCV-2 and HCV-3 patients were considered separately. **CONCLUSION:** SVR was associated with a reduction in HOMA-IR in patients infected with

HCV-1 but not HCV-2/3. This suggests that HCV-1 may play a causal role in the development of IR, which may be reversed by viral eradication.

Assessment of serum HCV RNA at week 12 post - treatment is as relevant as week 24 to predict SVR in patients with chronic hepatitis C treated with Pegylated interferon plus ribavirin. M.Martinot-Peignoux¹; S.Christianne¹; R.Marie Pierre²; L.Leclere¹; et al. Program Number: 118

Sustained Virologic Response (SVR), in patients with chronic hepatitis C treated PEG-IFN plus RBV is defined by undetectable serum HCV RNA at the end of the 24 weeks post-treatment follow-up period. Once achieved SVR is durable. Post-treatment viral kinetics in patients with Virologic Relapse (VR) remains unexplored. **The aim** of our study was to evaluate if the measurement of serum HCV-RNA at 12 weeks post-treatment could be as relevant as 24 weeks to assess SVR in patients receiving the combination PEG-IFN and RBV and to assess viral kinetics of VR. Patients: 675 patients, treated with PEG-IFN (304 treated with PEG-IFN 2a and 371 treated with PEG-IFN 2b) and RBV, with an end of treatment response. **METHODS:** Serum HCV-RNA was measured at 12 (W+12) and 24 (W+24) weeks, after treatment cessation. SVR was undetectable serum HCV-RNA at the end of post-treatment follow-up, VR reappearance of detectable HCV-RNA during post-treatment follow-up. We evaluated the positive predictive value (PPV) of undetectable serum HCV-RNA at W+12 to identify patients with SVR and kinetics of VR. HCV-RNA was measured with the VERSANTR HCV-RNA Qualitative Assay (TMA) and quantified with the VERSANTR HCV 3.0 Assay (bDNA) (Siemens). **RESULTS.** 573 patients had an available serum sample at W+12 and W+24 and studied. At the end of the 24 weeks post-treatment follow-up 408 (71%) patients demonstrated a SVR, 181 (71.2%) treated with PEG-IFN 2a, 227 (71.1%) treated with PEG-IFN 2b. At week+12 HCV-RNA was undetectable in 409 patients, 408/409 were SVR: PPV 99.7% (CI: 99.1%-100%). A subset of 482 patients had an available serum sample at W+4, HCV-RNA was undetectable in 417 patients, 407/417 were SVR; PPV 97.6% (CI; 96.1%-99.1%). Post-treatment viral kinetics of VR patients (table). **CONCLUSIONS.** Our results show that the assessment of serum HCV-RNA 12 weeks after treatment cessation (PPV 99.7%) is as effective as 24 weeks to predict SVR. This result shows that post-treatment follow-up to identify patients with SVR or VR could be shortened to 12 weeks post-treatment, emphasizing a new definition for SVR. Interestingly, in patients with VR, viral load revert to basal level as early as 24 weeks after treatment cessation indicating a steady state of viral load. Identification of VR as early as W+4 could allow to retreat patients while viral load remain low.

Long - term Survival of Sustained Virologic Responders to Pegylated Interferon Therapy for Chronic Hepatitis C. N.Chandok¹; W.Kim¹; R.Pedersen²; et al. Program Number: 119

BACKGROUND/aim: The goal of therapy (Tx) for chronic hepatitis C virus (HCV) infection is sustained virologic response (SVR: HCV RNA negative 6 months after cessation of Tx). Long-term benefits of SVR have been presumed, but not well documented. We compared patient survival by virologic response. **METHODS:** Based on a database that prospectively tracked anti-HCV Tx, all patients who received pegylated interferon (p-IFN) were identified. Tx response was categorized into: (1) SVR, (2) relapse (R: HCV RNA negative at end of Tx, but no SVR), (3) non-response (NR: all others), (4) early termination (ET: Tx discontinuation before planned assessment at 12 or 24 weeks). Survival information (death or liver transplantation) was extracted from medical records as well as the National Death Registry (Accurint system). **RESULTS:** Between 03/01 and 10/08, 515 patients received standard p-IFN Tx, mostly in combination with ribavirin(RBV). Genotype 1 (G1) was most common (64%), followed G2 (15%), G3 (15%) and others (5%). SVR was reached in 46% (34% for G1, 78% for G2, 65% for G3 and 48% for other). In the figure, SVR was associated with significantly lower mortality (5-year Kaplan-Meier mortality=3%, hazard ratio=0.26, p<0.01) compared to R(12%), NR(12%), or ET(19%). When the analysis was stratified by cirrhosis, which

was associated with higher mortality and lower SVR, no benefit in survival from SVR was found among patients with cirrhosis (5 year mortality: SVR=22.3% versus non-SVR=26.3, $p=0.71$). In contrast, in patients without cirrhosis, SVR led to decreased mortality (5 year mortality: SVR=1.2% versus non-SVR=6.5%, $p=0.01$). Thus, the number needed to treat in non-cirrhotic HCV patients to avoid one death within 5 years was 19. **CONCLUSION:** To our knowledge, this is the first evidence that p-IFN (in combination with RBV) leads to improved survival in patients who achieve SVR.

Diabetes Related Mortality in Patients with Chronic Liver Disease. N.Rafiq^{1,2}; M.Stepanova^{1,2}; H.M.Mir¹; et al. Program Number: 186

BACKGROUND: Increasing data suggests that type 2 diabetes (DM) can negatively impact the outcomes of patients with chronic liver disease (CLD). **AIM:** To assess cause-specific mortalities and their predictors in patients with CLD. **METHODS:** We utilized Third National Health and Nutrition Examination Survey (NHANES III) and Linked Mortality Files. Etiology of liver disease was determined based on positive serologic tests or available clinical data (+HCV RNA, +HBsAg, elevated iron studies, excessive alcohol consumption and clinical NAFLD). Patients with CLD were compared to those without liver disease (controls) using Rao-Scott chi-square statistics. Adjusted hazard ratios (AHR, 95% CI) for overall mortality and cause-specific mortality were calculated. Cox proportional hazard model was used for calculation of AHR for independent risk factors for overall mortality and cause-specific mortalities. Metabolic syndrome (MS) and its components were defined according to ATP-III criteria. Insulin resistance (IR) was defined as HOMA >3.0 . **RESULTS:** The study cohort included 15,866 individuals from NHANES III with complete data. Of these, 1972 patients had documented evidence for CLD and 13,004 were defined as controls without liver disease. CLD patients were more likely to be male (56.5% vs. 45.7%, $p<0.0001$), non-Caucasians (27.3% vs. 22.9%, $p=0.0002$) and smokers (34.5% vs. 26.6%, $p=0.0004$). CLD patients had higher BMI (27.1 vs. 26.4, $p<0.0001$) and were more likely to have DM (8.10.8% vs. 5.50.3%, $p=.0005$), MS (30.31.4% vs. 25.80.8%, $p=0.0001$) and IR (34.42.1% vs. 22.50.9%, $p<0.001$). After an average follow up of 8.5 years, 245 CLD patients and 1842 controls died. After adjusting for components of MS, patients with CLD had higher AHR for overall mortality (1.339, 95% CI 1.337-1.342), liver-related mortality (10.536, 95% CI 10.459-10.613), DM-related mortality (5.580, 95% CI 5.545-5.615) and solid organ malignancy-related mortality (1.272, 95% CI 1.267-1.276) but not cardiovascular mortality (0.747, 95% CI 0.745-0.750). Furthermore, after adjusting for other potential confounders, IR and DM were independent predictors of overall mortality and cause-specific (Liver, DM, Malignancy)-mortality in patients with CLD. **CONCLUSIONS:** CLD patients have higher diabetes related mortality. Additionally DM and IR are independent risk factors for overall and cause-specific mortality in CLD patients.

Combination Therapy With A Nucleoside Polymerase (R7128) And Protease (R7227/ITMN - 191) Inhibitor In HCV: Safety, Pharmacokinetics, And Virologic results

From INFORM – 1. E.J.Gane⁴; S.K.Roberts⁵; C.A.Stedman⁶; et al. Program Number: 193

INTRODUCTION: HCV regimens of multiple oral direct acting antivirals (DAAs) may offer advantages by enhancing potency, reducing the emergence of resistance, and potentially eliminating the need for PEG-IFN and/or ribavirin. R7128/R7227 is a particularly attractive combination due to the differing mechanisms of action, different routes of elimination, and high barrier to resistance. **METHODS:** INFORM-1 is a randomized, double-blind, placebo controlled, ascending dose trial. HCV-infected adults (Genotype 1, Treatment nave, experienced, and null responder cohorts) received up to 14d oral combination therapy. Two initial groups received low dose monotherapy with R7128 (n=8) 500mg bid or low dose R7227 (n=9) 100mg tid on d1-3, both followed by combination R7128/R7227 on d4-7. Further groups received 14d escalating doses of R7128/R7227. R7128 was given as 500 or 1000mg bid, R7227 either 600 or 900mg bid or 100 or 200mg tid. After

completion of 14d R7128/R7227, pts received Pegasys/Copegus (SOC). Safety, viral kinetics, resistance, & PK of R7128/R7227 were evaluated in all subjects. **RESULTS:** 63 pts have completed R7128/R7227 dosing, which was well-tolerated with no treatment-related SAEs, dose modifications, or discontinuations reported. The antiviral responses following 14d R7128/R7227 combination are summarized in Table 1. There were no apparent differences in antiviral responses between nave and experienced pts, between tid or bid R7227 regimens, or between Genotype 1a and 1b pts. Out of 53 pts receiving active R7128/R7227, only 1 experienced viral rebound, defined as > 0.5 log₁₀ increase from nadir; this subject had an end of treatment HCVRNA = 3070 IU/mL, and remains undetectable after 12wks SOC. Final results from all pts will be presented. **CONCLUSION:** The combination of R7128/R7227 for up to 14d provided significant antiviral potency in treatment nave and experienced patients, sustained viral reductions, and appears safe and well-tolerated as a twice daily oral regimen. This promising combination is undergoing further development for the treatment of CHC.

Obesity Worsens the Natural History and Predicts Clinical Decompensation (CD) in Patients (pts) with Compensated Cirrhosis. A.Berzigotti^{2,3}; G.Garcia-Tsao^{1,4}; J.Bosch^{2,3}; et al. Program Number: 205

Obesity is a fast-growing health issue even among pts with cirrhosis. Obesity-related cirrhosis appears to have a lower survival than HCV cirrhosis (Hepatology 2002;35:1485). We have shown that portal hypertension (as determined by hepatic venous pressure gradient, HVPG), albumin and MELD are independent predictors of CD in compensated cirrhosis (Gastroenterology 2007; 133:481). The effect of obesity on the development of CD in pts with cirrhosis of any etiology has not been investigated and is the aim of this study. **METHODS:** A cohort of 123 compensated cirrhotics without varices in whom data for body mass index (BMI) was available and that were included in a trial evaluating β -blockers in preventing varices (NEJM 2005;353:2254) was analyzed. All had baseline laboratory tests and HVPG. Pts were followed until development of varices or variceal hemorrhage (VH) or end of study. The endpoint was CD (development of ascites, hepatic encephalopathy or VH). **RESULTS:** Of 123 pts, 30 (24%) had normal BMI (NL, BMI <25), 54 (44%) were overweight (OW, BMI 25-29.99) and 39 (32%) were obese (OB, BMI >30). The only baseline parameter different among groups was etiology of cirrhosis, with lower viral and greater alcoholic and cryptogenic in OB. In a median followup of 59 (1-109) months, 31 (25%) developed CD (NL:13%, OW:20% and OB:41%, p=0.018). Probability of developing CD (Kaplan Meier) was significantly greater in OB (Figure). By Cox regression, independent predictors of CD were: HVPG [HR: 1.12 (95%CI 1.05-1.21)]; albumin [HR 0.37 (0.17-0.81)] and obesity [HR 3.21 (1.56-6.60)]. MELD and treatment group were not significant. **CONCLUSIONS:** This study is the first to demonstrate the deleterious effect of obesity, independent of MELD, on the natural history of compensated cirrhosis of all etiologies and suggests that weight reduction should be an important therapeutic measure in this patient population.

Significant Decline in Liver Stiffness during Four Years of Follow - up among Patients Cured for Hepatitis C. E.S.Andersen¹; B.K.Moessner²; P.B.Christensen^{2,3}; M.S.Kjaer⁴; N.Weis¹ Program Number: 213

BACKGROUND and AIMS: Within the last few years, it has been shown that fibrosis may regress after successful treatment for HCV. Transient elastography is a novel non-invasive technique that in several studies has been accurate for detection of fibrosis and cirrhosis. Using that technique, we have studied how often and to which degree fibrosis regresses. **METHODS:** 114 patients treated for HCV with Interferon and Ribavirin in four hospital departments in Denmark were included in the study from May 2007 to May 2009. Inclusion criterion was a liver biopsy classified by Metavir scale prior to treatment during 1996-2008. The patients were examined with transient elastography for regression of fibrosis. Successful liver stiffness measurements (LSM) (valid measurements >

60%, IQR < 25%) could not be obtained for ten of these patients (8.8%). Of the remaining 104 patients (65 males/39 females, age 53 (47-58) years (median(IQR)), BMI 25.0 (22.4-28.0) kg/m², 66 patients (63.4%) had sustained virological response (SVR), 10 patients (9.6%) had relapse after treatment, and 28 patients (26.9%) were non-responders. The median follow up time was 47 (27-74) months for SVR and 48 (31-73) months for non-SVR (p=0.44). Conversion from LSM to the Metavir scale was performed with cut-off values 7.7 kPa for F2 and 13.0 kPa for F4 for statistical calculations. **RESULTS:** LSM was significantly lower for patients with SVR versus non-SVR (p<0.001) using the Cochran-Mantel-Haenszel test. Overall median LSM was found to be 5.6 (4.8-7.1) kPa for patients with SVR, vs. 11.1 (7.2-24.8) kPa for non-SVR. Among 19 patients with F4 prior to treatment and SVR, 57.8% (11) had LSM less than 7.7 kPa (F0/F1), 36.8% (7) had between 7.7 kPa and 13.0 kPa (F2/F3), and 5.3% (1) had above 13.0 kPa (F4). Among patients with F2/F3 before treatment and SVR as treatment outcome, 92.9% (26) had LSM less than 7.7 kPa (F0/F1) and 7.1% (2) had between 7.7 and 13.0 kPa (F2/F3). None had more than 13.0 kPa (F4).

CONCLUSION: LSM was significantly lower for patients with SVR than for non-SVR after treatment with Interferon and Ribavirin, indicating that fibrosis in most cases regresses in patients successfully treated. 57.8% of cured patients with cirrhosis prior to treatment were found to have normal liver elasticity and only 5.3% still had a LSM compatible with cirrhosis.

Silibinin and Related Compounds are Direct Inhibitors of Hepatitis C Virus RNA - Dependent RNA Polymerase. A.Ahmed-Belkacem¹; N.Ahnou¹; L.Barbotte¹; et al. Program Number: 226

Only approximately 50% of patients with HCV genotype 1 infection eradicate infection upon pegIFN-ribavirin therapy. Current HCV drug discovery efforts focus on developing molecules that specifically inhibit HCV enzymes, such as the RNA-dependent RNA polymerase (RdRp) or the NS3/4A protease. Silymarin is a mixture of flavonolignans extracted from the milk thistle, which contains several molecules including silibinin A, silibinin B, isosilibinin A, isosilibinin B, silichristin, and silidianin. Intravenous infusion of Legalon SIL, a commercially available preparation of silibinin, induces dose-dependent reduction of HCV RNA levels. Our aim was to test the isomers contained in silymarin preparations for their ability to inhibit HCV enzymatic functions and replication in different models. **METHODS:** The inhibitory activity of silymarin components was tested in HCV RdRp and NS3/4A protease enzyme assays. Their ability to inhibit replication of an HCV genotype 1b replicon and the JFH1 infectious HCV model in cell culture was also studied. The effect of amino acid substitutions known to confer HCV resistance to RdRp inhibitors was tested.

RESULTS: Silibinin A, silibinin B, their water-soluble dihydrogen succinate forms and Legalon SIL, a commercially available intravenous preparation of silibinin, inhibited HCV RNA-dependent RNA polymerase function, with inhibitory concentrations 50% (IC₅₀s) of the order of 75-100 micromolar. Silibinin A and silibinin B also inhibited HCV genotype 1b replicon replication with effective concentrations 50% (EC₅₀s) of the micromolar order, and HCV genotype 2a strain JFH1 replication in cell culture with EC₅₀s approximately one log above those observed in the replicon system. None of the tested silymarin components showed any inhibitory activity in the NS3/4A protease assay, up to a concentration of 200 M. No cytotoxic effect was observed at inhibitory concentrations in two different human cell lines (Huh7 and HEK 293). Amino acid substitutions known to confer resistance to RdRp inhibitors, including 2'-methyl nucleoside analogues (S282T) and non-nucleoside inhibitors (P495L, M423T, H95Q, and C316Y, located in thumb 1, thumb 2, palm 1 and palm 2 RdRp domains, respectively) did not confer resistance to silibinin in the RdRp enzyme assay. **CONCLUSIONS:** Silibinin A and silibinin B, as well as Legalon SIL, inhibit HCV replication in cell culture. This effect is at least partly explained by the ability of these compounds to directly inhibit HCV RdRp activity. These results provide a basis for the optimization and subsequent development of members of the Flavonoid family as specific HCV antivirals.

PegInterferon Alfa - 2a With or Without Ribavirin RESULTS in Minimal Effect on Quality of Life, Emotional, and Cognitive Outcomes: RESULTS of the Peds - C Trial. J.R.Rodrigue1; W.F.Balistreri2; B.Haber3; et al. Program Number: 238

BACKGROUND: Interferon (IFN) therapy in adults with HCV infection is associated with quality of life, emotional, and neurocognitive deficits. However, how IFN affects these functional domains in children is largely unknown. **Aim:** To prospectively assess the impact of IFN and IFN+ribavirin on the QOL, behavioral, emotional, and cognitive functioning of children with HCV. **METHODS:** We studied 114 children enrolled in a placebo-controlled, randomized, multi-site clinical trial evaluating pegIFN -2a alone (mono, n=59) or with ribavirin (combo, n=55) (Peds-C trial). At time of enrollment, all children underwent a baseline assessment that included the Child Health Questionnaire (CHQ), Child Behavior Checklist (CBCL), Child Depression Inventory (CDI), and Behavior Rating Inventory of Executive Function (BRIEF). Assessments were repeated at Week 24 and Week 48 after treatment initiation. **RESULTS:** At entry, mean age was 10.73.4 yr, 45% female, and 75% White. The most common mode of transmission was vertical/perinatal (77%), HCV genotype was predominantly Type 1 (81%), median infection duration was 117.2 months, mean ALT was 5948, and children were HCV RNA positive for at least 6 months. From baseline to Week 24, children in both the mono and combo groups experienced a significant decline in the CHQ Physical Summary Score (mean = 2.247.9, $p = 0.042$ and = 2.406.8, $p = 0.013$, respectively). There were no significant changes from baseline to Week 24 on measures of behavior (CBCL), depression (CDI), or cognitive functioning (BRIEF) for children in either the mono or combo group. At Week 48, children in the combo group had significantly fewer Internalizing and Total behavior problems, relative to baseline scores (mean = 4.069.4, $p = 0.02$ and = 3.388.1, $p = 0.025$). No other significant changes were noted from baseline to Week 48. **CONCLUSIONS:** PegIFN alone or in combination with ribavirin does not lead to clinically significant changes in overall quality of life, behavior problems, depression, or cognitive disturbance in children.

HCV clearance after PEG IFN plus RBV improves the course of HCV cirrhosis regardless of portal hypertension. V.Di Marco1; V.Calvaruso1; S.De Lisi1; et al. Program Number: 345

BACKGROUND and AIMS: To assess whether clearance of HCV RNA induced by antiviral therapy at an advanced stage of disease improves the long-term outcome of cirrhosis. **Patients and METHODS:** We followed a prospective cohort of patients with compensated HCV cirrhosis with or without esophageal varices treated with Peg-interferon alfa-2b (55: 1 mg/kg/wk, 303: 1.5 mg/kg/wk) and ribavirin 1-1.2 g/die. All were screened for varices before treatment and followed by ultrasound every six months. The Kaplan-Meier method was used to estimate the effect of SVR on development of decompensation or HCC and groups were compared by using log-likelihood tests. Cox regression analysis was used to determine which baseline factors were associated with development of decompensation, death or HCC. **RESULTS:** A cohort of 358 patients was prospectively enrolled since 2001. All patients have more than 24 months of follow-up. Seventy-nine (22%) achieved SVR. The median follow-up was 40 months. During this period 3 patients with SVR and 76 without SVR decompensated ($p = 0.001$). One patient with SVR and 78 without SVR developed HCC ($p = 0.02$). By multivariate analysis presence of esophageal varices (OR 3.73 CI: 1.74 - 7.99; $p = 0.001$), platelets below 90,000 mm³ (OR 1.94 CI: 1.10 - 3.44; $p = 0.023$), Child Pugh score = 6 (OR 2.79 CI: 1.62 - 4.83; $p < 0.001$), and absence of SVR (OR: 4.36 CI: 1.35 -14.12; $p = 0.014$) were independently associated to decompensation. The variables independently associated to development of HCC were male gender (OR 2.90 CI: 1.19 - 7.07; $p = 0.019$), platelets below 90,000 mm³ (OR 2.97 CI: 1.44 - 6.13; $p = 0.003$) and absence of SVR (OR 10.10 CI: 1.37 - 74.35; $p = 0.023$). Liver related mortality was independently associated to platelets below 90,000 mm³ (OR 2.85 CI: 1.37 - 5.92; $p = 0.005$) and absence of SVR (OR 8.59 CI: 1.17 - 63.08; $p = 0.035$). **CONCLUSIONS:** SVR after antiviral treatment obtains a meaningful reduction in the rate of hepatic decompensation, of HCC and of liver-related deaths in patients with

compensated HCV cirrhosis, regardless of the presence of portal hypertension at the time of starting treatment.

Impact of tobacco and alcohol consumption on 3 - month morbidity following liver transplantation among patients who consumed alcohol and smoked tobacco whilst on the waiting list. P.Perney¹; F.Sgalas-Largey²; G.Chanques²; et al. Program Number: 573

INTRODUCTION We have recently reported that about 10% of cirrhotic patients (pts) on the waiting list for liver transplantation (LT) consume alcohol, and 40% are smokers. The aim of our study was to assess the impact of alcohol and tobacco consumption on mortality rate and morbidity during the first 3 months following LT among pts who smoked tobacco and consumed alcohol whilst on the waiting list for LT. **PATIENTS AND METHODS** From May 2005 to December 2008, during pre-transplant evaluation, all cirrhotic pts (whatever the cause of cirrhosis) systematically had a consultation with a specialist in addictology who did not belong to the transplantation team. The data concerning the pre-operative period and the first 3 months following LT were collected from medical files. The post-operative data were: mortality and morbidity criteria including length of stay in ICU; acute rejection; infectious, biliary, pulmonary, and cardiovascular diseases. Moreover, we assessed the consumption of alcohol, tobacco, and illicit drugs before and after inscription on the waiting list. **RESULTS** Among the 142 pts who were registered on the waiting list, 78 were transplanted: 65 males and 13 females (mean age 53+/-9.7 years). The aetiologies of cirrhosis were: alcohol n=50; HCV n=15; HBV n=2; others n=11. The mean MELD score was 13.8+/-6.5. We diagnosed regular alcohol consumption in 9 pts (11.5%) on the waiting list (8 men, 1 woman). The mean alcohol consumption was 13+/-5 g/day. There was no difference for either aetiology or gravity of cirrhosis between pts who consumed alcohol and those who did not. Alcohol consumption did not increase the mortality rate, the length of stay in the ICU or the risk of post-surgical morbidity. Thirty-three pts on the waiting list were smokers (42.3%). Among those who did not smoke (n=45), 24 had stopped tobacco consumption when they were registered on the waiting list. Smokers were younger (50 vs 55 years, p=0.01), and presented more often with chronic obstructive pulmonary disease (27% vs 5%, p=0.008). Tobacco consumption in pts on the waiting list was associated with higher morbidity rate: increased risk of bacterial cholangitis: 13/33 vs 8/45 (p=0.03), of biliary stenosis: 15/33 vs 9/45 (p=0.02), and a greater need of sedative treatments (p=0.03). Moreover, there was a trend to increased length of stay in the ICU for smokers (15 vs 11 days, p=0.09). Finally, pts who stopped tobacco consumption whilst on the waiting list exhibited no more post-operative complications than those who had never smoked. **CONCLUSION** Tobacco withdrawal whilst on the waiting list reduced the over-morbidity risk associated to tobacco and must be encouraged.

The Natural History of Hepatitis C Treatment Failures: A Meta – Analysis. A.Singal¹; M.L.Volk¹; D.M.Jensen²; et al. Program Number: 731

INTRODUCTION: Over 50% of genotype 1 hepatitis C (HCV) patients fail to respond to pegylated interferon (PEG-IFN) and ribavirin (RBV) combination therapy. The natural history of treatment failures versus patients who achieve sustained virologic response (SVR) is an important factor when considering re-treatment. **AIMS:** To quantify the incidence of liver-related morbidity and mortality (decompensated cirrhosis, hepatocellular carcinoma, and liver-related death) among HCV patients who do not achieve SVR after treatment ("treatment failure"). To compare the incidence of liver-related morbidity and mortality among patients who achieve SVR to those who fail interferon-based treatment. **METHODS:** An electronic search on MEDLINE and EMBASE from 1966 to 2008, supplemented with a manual search of references from review articles, identified all English language trials that reported liver-related morbidity and mortality outcomes stratified by SVR status. Subset analysis among HCV patients with advanced fibrosis or cirrhosis was performed. Two investigators extracted all necessary data, and the pooled relative risks of all outcomes were

computed using a random effects model. **RESULTS:** A total of 26 studies were included in the meta-analysis. HCV patient with SVR were significantly less likely than treatment failures to develop liver-related mortality (RR 0.24; 95% CI: 0.15-0.37), hepatocellular carcinoma (RR 0.24; 95% CI: 0.19-0.31), and hepatic decompensation (RR 0.22; 95% CI: 0.08-0.56). Among treatment failures with advanced fibrosis, rates of liver-related mortality (2.73%/year; 95% CI: 1.38-4.08), hepatocellular carcinoma (3.22%/year, 95% CI: 2.02-4.42), and hepatic decompensation (2.92%/year; 95% CI: 1.61-4.22) were substantial. Among treatment failure patients, non-responders to therapy were more likely to get hepatocellular carcinoma compared to relapsers (RR 2.37; 95% CI: 1.31-4.29). **CONCLUSIONS:** Patients with hepatitis C who achieve SVR have significantly lower liver-related morbidity and mortality than treatment failures. Rates of liver-related morbidity and mortality are substantial in patients with advanced fibrosis or cirrhosis who fail HCV treatment.

Self - Management Interventions for Veterans with Hepatitis C. E.J.Groessl^{1,2};

K.R.Weingart¹; A.L.Gifford^{4,5}; S.Asch³; S.B.Ho^{1,2} Program Number:

BACKGROUND: Chronic hepatitis C (HCV) infection affects almost 2% of the US population and 5 - 6% of veterans receiving care at VA facilities. Antiviral treatment is available for chronic HCV but it has side effects, is not offered to everyone, and is successful less than half the time. Self-management interventions are one option for improving the health-related quality of life of HCV-infected individuals. Objective: To examine the efficacy of a self-management intervention for VA patients with chronic HCV. **METHODS:** 137 VA patients were recruited via healthcare providers and flyers. Participants (mean age of 54) were 95% male, 59% Caucasian, 17% married, 68% attended some college, 70% unemployed or disabled. They were randomized to either usual care or a weekly self-management workshop lasting 6 weeks. The six 2-hour self-management sessions were co-led by a peer-leader and a health care professional. The intervention is based on cognitive-behavioral principles and was adapted from an existing self-management framework that has been efficacious with other chronic diseases. HCV-specific modules were added. Outcomes including generic and disease-specific HRQOL, HCV knowledge, self-efficacy, depression, energy, and health distress were measured at baseline and again 6 weeks later. Data were analyzed using repeated measures ANOVA. **RESULTS:** Significant differences were in found between the intervention groups over time on the HQLQ - health distress ($p=.017$), SF-36 energy ($p = .040$), HCV Knowledge ($p < .001$), HCV self-efficacy ($p = .040$) indicating that the intervention produced health benefits. A number of other variables showed trends toward significance: Depression ($p = .093$); SF-36 physical functioning ($p = .055$). Despite a very short follow-up period to date, early data on the proportion of patients that went on to get antiviral treatment indicate that 5/69 (7.2%) patients in the self-management program have initiated antiviral treatment while 3/63 (4.7%) initiated antiviral treatment in the education-only intervention. **CONCLUSION:** HCV-infected VA Patients attending the Hepatitis C Self-Management Program had better outcomes than the comparison group in a number of different areas. Plans for implementing the intervention at other VA and community settings are being developed. results on additional outcomes such as health care utilization and antiviral treatment are forthcoming.

Formal HCV Patient Education is Effective in Improving Patient Knowledge of HCV Disease in Vulnerable Populations. M.E.Surjadi^{1,2}; C.Ayala^{1,2}; H.F.Yee^{1,2}; M.Khalili^{1,2}

Program Number: 740

There are substantial racial disparities in the prevalence of chronic HCV disease and its complications. The evaluation of HCV knowledge and effectiveness of formal patient education is crucial in understanding the means to reduce disparity in HCV disease prevalence and potentially its outcome in vulnerable populations. **AIM:** To assess baseline knowledge and impact of a formal HCV education as well as factors associated with improved HCV knowledge in the vulnerable populations. **METHODS:** Over 18-months, 201 HCV-infected patients underwent a 2-hour

standardized formal group education at a county hospital. Patients completed detailed demographic and pre- and post-education questionnaires (score=31) with respect to HCV knowledge, natural history, transmission, diagnosis, treatment, and health care maintenance. Statistical analysis included descriptive analysis, Wilcoxon Signed-Rank test, and regression modeling. **RESULTS:** Patient characteristics were: 69% male, mean age 49.10, 49% White (26% AA, 10% Latino), 75% unemployed, 52% with some college education, 64% used IVDU (16% on methadone), 57% used 50 g/day of alcohol, and 7% were HIV coinfecting. On univariate analysis, higher pre-education test score was associated with younger age (coef 0.6, $p<0.0001$), White race (coef 5.3, $p<0.0001$), higher education (coef 1.3, $p=0.002$), shorter IVDU duration (coef 0.4, $p=0.02$), shorter alcohol duration (coef 0.5, $p=0.003$), and interest in obtaining medical care (coef 2.14, $p=0.03$). Following HCV education the overall test scores improved significantly by 14% ($p<0.0001$) specifically in the areas of HCV transmission ($p=0.003$), HCV general knowledge ($p=0.02$), and health care maintenance ($p=0.004$). On multivariate analysis, White (vs. non-White) race (coef 0.087, $p=0.01$) and interest in obtaining medical care (coef 4.25, $p=0.002$) were associated with higher test scores prior to HCV education. Interest in obtaining medical care (coef 0.7, $p=0.001$) was the only independent predictor of improvement in test scores following education. **CONCLUSIONS:** Formal HCV education is effective in improving HCV knowledge in vulnerable populations. Although White race and interest in obtaining medical care were predictors of having more knowledge about HCV disease prior to receipt of HCV education, all patients independent of racial background have a significant improvement in their knowledge about HCV disease after a formal patient education. Promoting effective HCV educational programs among non-White populations may be an important factor in reducing the racial disparities in HCV prevalence and disease outcome. Dr. Khalili is supported by R01DK074673, ADA 1-07-CR-70 grants.

Targeted screening for viral hepatitis in an Italian community of 100.000 inhabitants.

C.Zani³; L.Pasquale²; M.Bressanelli³; B.Paris²; et al. Program Number:

PURPOSE. The optimal approach to detecting HCV and HBV infection is to screen persons for a history of risk of exposure to the virus and to test selected individuals who have an identifiable risk factor. Vallecantonica is an Italian province with 99872 inhabitants with a mortality for HCC and cirrhosis that is almost twice the regional data. The Vallecantonica, Health Authority promoted a targeted screening for HCV, HBV infections identifying persons at risk according to international guidelines. The initiative involved all the general physicians and an advertising policy to the general population. The aim of this study is to estimate the prevalence of chronic liver diseases (CLD) and hepatocellular carcinoma (HCC) that resulted from this targeted screening. **METHOD.** In Italy, health cares are provided to each individual by the National Health Service and all data are recorded on computer files, using a unique individual code, so as record linkage operations can be done. We used the following sources of data, linked at the individual level: 1) hospital discharge data; 2) outpatients of Viral Hepatitis Services; 3) tests for anti-HCV antibodies and HBsAg; 4) Local Health Authority (LHA) registry of CLD patients; 5) drug prescriptions; 6) patients treated with anti-HBV or anti-HCV therapy; 7) patients admitted to the LHA Alcohol Clinic. We used the International Classification of Disease (ICD), IX version, for each database. When more than one diagnosis were available for a subject, we used the most severe diagnosis. Patients with hepatic enzymes alterations only and without diagnosis of liver disease were classified as chronic hepatitis cases. All the data are referred to 31st December 2007. **RESULTS.** Among subjects aged 25 years and over, 50.2% and 46.4% had at least one test for HCV and HBV infection respectively. HCC was found in 2.6% of anti HCV+, cirrhosis in 11.3%, chronic hepatitis in 83.5%. HCC was found in 2.8% of HBsAg+, cirrhosis in 6.7%, chronic hepatitis in 88%. The prevalence of HCV infection increased with age with the highest value among subjects over 65 years (8.8 %). For HBV infection, the highest prevalence was found in subjects of 55-64 years group (4.4%). A total of 3.3% of the population were affected by CLD or HCC, (4.1% males and 2.6% females). **CONCLUSION.** These results suggest that a

targeted screening policy is feasible in a large community and that it could identify most of the patient with liver diseases. In addition this study provided estimates of the prevalence of liver diseases, using various sources of routinely collected data, linked at the individual level.

Project ECHO (Extension for Community Healthcare Outcomes) : Knowledge Networks Expand Access to Hepatitis C (HCV) Treatment with Pegylated Interferon and Ribavirin in Rural Areas and Prisons. Care is as Effective as a University HCV Clinic. S.Arora1; G.H.Murata1; K.A.Thornton1; et al. Program Number: 747

PURPOSE: To conduct a prospective cohort study to evaluate the efficacy of HCV treatment by primary care providers in rural areas and prisons in comparison to university clinics.

METHODS: Project ECHO is a new method of healthcare delivery and clinical education for the management of complex, common and chronic diseases, in underserved areas, using HCV as a model. In a worldwide competition sponsored by Ashoka Foundation and Robert Wood Johnson Foundation, Project ECHO was selected as the most disruptive innovation in healthcare that can improve healthcare globally. The Project ECHO Hepatitis C initiative is a partnership of University of New Mexico, eight prisons and fourteen rural health clinics dedicated to providing best practices and protocol-driven healthcare in rural areas. Telemedicine and internet connections enable specialists to co-manage HCV patients using case-based knowledge networks and to track outcomes. Project ECHO was Project ECHO partners (nurse practitioners, primary care physicians, and physician assistants) present HCV positive patients during weekly 2-hour telemedicine clinics using a standardized, case-based format that includes discussion of history, physical examination and test results. In these case-based learning clinics, partners rapidly gain deep domain expertise in HCV as they collaborate with university specialists in hepatology, psychiatry and substance abuse in co-managing their patients. **RESULTS:** Since 2003, 395 HCV knowledge network clinics have been conducted with 3965 case presentations. 3812 hours of Hepatitis C related no cost CME credits have been awarded to rural providers. 340 patients that met the study inclusion/exclusion criteria have terminated their treatment for hepatitis C (236 at a Project ECHO site and 104 at UNMH). Their mean age was 43.5 ± 10.5 years, 62.4% were male, and 58.7% were members of a minority group (mostly Hispanic). Of the 280 subjects whose final status has been determined, 152 were free of virus at 6 month follow-up. No difference was found in the cure rate for Project ECHO sites versus UNM (52.6% versus 58.3%). Project ECHO sites were more likely to treat minorities (63.9% versus 47.1%; P=0.004) and Hispanics (56.1% versus 34.3%; P<0.001) than the University. Significant adverse events (SAE) occurred in 11.2% of patients. Female gender, a high globulin, advanced age, and low BUN, were predictive of development of an SAE. Primary care providers experienced significant improvement in self efficacy and professional satisfaction(p<0.0001).

CONCLUSIONS: ECHO based HCV treatment for rural patients and prisoners is as effective as a university HCV clinic.

Dimensions of Fatigue are Associated with Learning, Memory and Motor Deficits Among People Infected with the Hepatitis C Virus (HCV). C.Posada; F.Barakat; D.J.Moore; et al. Program Number: 756

Individuals with HCV often complain of fatigue and cognitive deficits. The present study examines the relationship between specific dimensions of fatigue and specific aspects of HCV disease (e.g, liver disease severity, biomarkers and neurocognitive abilities). **METHOD:** We examined 16 HCV+ men and 26 HCV+ women with the Multidimensional Fatigue Inventory Short Form (MFISI-SF) and the Fatigue Severity Scale (FSS). The MFISI-SF has 5 subscales scores (general, physical, emotional, mental and vigor), and a total score. The FSS is a 9 item scale that measures severity of fatigue. We also administered a neuropsychological battery that assessed 7 cognitive domains. Median age was 50 (range 22 to 66), the median (log) HCV RNA was 5.8 (range 4.6 to 6.9), and the AST-to-Platelet Ratio Index (APRI) median was 0.56 (range 0.1 to 5.9). **RESULTS:** Statistically

significant correlations were found between fatigue and neuropsychological deficits. Greater general fatigue correlated with greater learning deficits, greater physical fatigue correlated with greater motor deficits, whereas increased vigor correlated with greater learning and recall deficits. Interestingly, worse severity of fatigue correlated with learning, recall, and global neuropsychological deficits (see Table). No other neuropsychological deficit scores correlated with fatigue. Levels of HCV RNA and APRI, as well as a lifetime diagnosis of Major Depressive Disorder did not significantly correlate with severity of fatigue (all $p > 0.10$). **SUMMARY:** In patients with HCV: 1) severity of fatigue appears to be associated with neuropsychological deficits especially in learning and recall; 2) physical fatigue was associated with greater motor deficits; 3) there was no correlation between viral load, disease stage, or fatigue in this cohort. Further assessment is necessary to determine whether fatigue and learning/memory difficulties are the result of a common HCV-induced pathway or whether the two may occur independently.

Neurocognitive Function and Mood Changes in HCV patients: Effect of Disease Severity.

F.Barakat; M.Cherner; D.L.Oliver; et al. Program Number: 757

Chronic Hepatitis C (CHC) is alleged to reduce Quality of Life (QOL) and in some patients is associated with cognitive dysfunction. However, it is unclear whether disease severity affects QOL and cognition. **The aim** of this prospective study was to describe the QOL and neurocognitive (NC) changes in CHC patients prior to IFN based therapy and to explore the disease severity on these changes. **METHODS:** 152 consecutive patients were evaluated for therapy between 2005 and 2007. The subjects of this analysis are 89 patients who completed a pre-IFN therapy assessment. Two NC summary measures were analyzed: a neuropsychologist clinical assessment whether impairment was present or not and a demographically adjusted Global Deficit Score (GDS), which captures degree of impairment. GDS scores ≥ 0.5 were considered to indicate global NC impairment. Mood was assessed using the Beck Depression Inventory II (BDI) and the presence of the skills necessary for effective learning, communication and thinking was examined using the Wide Range Achievement Test (WRAT). **RESULTS:** The 89 patients had a mean age of 47.58.9 years; 46.1% were male, 41.6% Caucasian, 67.4% were Genotype 1 and all had compensated liver disease. The mean education was 12.32.2 years. 29.2% were co-infected with HIV. 84.3% had a history of drug abuse or dependence. 56.8%, 16.7% vs. 42% met the DSM IV criteria for lifetime abuse or dependence of ETOH, marijuana or cocaine respectively. 12% were diagnosed with ADHD and 15.7% with Antisocial Personality Disorder. 50% had a history of Major Depressive Disorder (MDD), while 17.9% had current MDD. NC impairment was detected in 27.9% of patients. The mean GDS score was 0.400.42, median total BDI was 12 (0-51) and WRAT score of 94.0 (48-122). Genotype 1 and co-infection with HIV did not play a role in NC impairment or mood changes. However, patients with severe fibrosis/cirrhosis had global NC impairment (0.240.20 vs. 0.500.50; $p=0.030$) and significantly more severe mood changes (8% vs. 18%; $p=0.043$) than patients with mild/moderate fibrosis respectively. **CONCLUSIONS:** In CHC patients with compensated liver disease and prior to anti-viral therapy: 1) 28% had NC deficits; 2) 22.4% had moderate to severe depression and 3) advanced disease stage was associated with worsening NC function and mood changes. These data underscore the importance of early HCV therapy. The study remains in progress in collaboration with the HNRC Group and NIDA Program Project.

Use of Telemedicine and the "Warm Line" for the Treatment of Hepatitis C Infection (HCV) in the Correctional Setting to Reduce Barriers to Specialty Care.

P.Nachin; M.Kerbleski; A.Gaglioti; et al. Program Number: 758

BACKGROUND: The seroprevalence of HCV is estimated to be approximately twenty times higher in the incarcerated population than the general population. Up to 35% of inmates have chronic HCV (Hunt and Saab, 2009). The prevalence of cirrhosis in incarcerated populations is unknown. Purpose To identify, triage, and treat patients with chronic hepatitis C (HCV) within the

California Department of Corrections and Rehabilitation (CDCR) and to estimate the prevalence of cirrhosis and end stage liver disease in this population. **METHODS** In May, 2008, the California Prison Health Care Services (CPHCS) collaborated with the University of California San Francisco Correctional Medicine Consultative Network (CMCN) to improve access to HCV treatment in California state prisons. A multidisciplinary, primary care-based model using an evidence-based approach to treatment and management of chronic liver disease was created. To increase capacity to treat HCV among primary care and nursing providers within CDCR, CMCN held a HCV training conference in October, 2008. Hepatologists treated patients via telemedicine in response to primary care provider-initiated referrals. The CMCN "warm line" was established to further assist CPHCS clinicians managing HCV. Consultations were requested by phone, fax, or e-mail to CMCN hepatology nurses. Warm line access was available weekdays during business hours and inquiries were answered within 24 hours. Hepatologists provided written consultation notes and faxed copies to each provider. A chart review of all telemedicine and warm line consultations was completed. Patients with liver biopsy results of Metavir stage 3-4 or platelet counts of <140,000 were assumed to have cirrhosis. **RESULTS** The CMCN hepatologists performed 441 new patient HCV telemedicine consults between May 2008 and May 2009. 569 warm line requests involving 433 patients were answered between November, 2008 and May, 2009. 25% of patients discussed were subsequently referred to telemedicine due to disease complexity. 186 of 766 patients (telemedicine had stage 3-4 fibrosis on biopsy or platelets <140,000. In our population (N=766), the estimated prevalence of cirrhosis was 24%. **CONCLUSION** Academic partnerships can facilitate access to HCV care for the incarcerated, an at-risk population. Use of telemedicine and warm line allow for efficient specialty access and cost containment while improving quality of care.

Hepatitis C Virus (HCV) Infection and Re - Infection in Illicit Drug Users. A.Barrieshee1; H.Tossonian1; J.Grebely4; et al. Program Number: 773

INTRODUCTION: Over 300,000 Canadians are living with chronic HCV infection, over half being current or former IDUs. The possibility of re-infection is often cited as a reason for not initiating treatment in this group of patients, although recent observational data suggest that the rate of re-infection may be reduced following spontaneous or treatment-induced virologic clearance, although such data are often retrospective and incomplete. With this in mind, we have undertaken a systematic, prospective study to evaluate the incidence of HCV viremia in IDUs at risk of new infection **METHODS:** We indentified a cohort of IDUs receiving care at the Pender Community Health Centre on Vancouver's Downtown East Side. Potential subjects were identified as either never having been infected with HCV (non-infected arm), having spontaneously cleared the virus (spontaneous arm), or having achieved a sustained virologic response on antiviral treatment (SVR arm). A questionnaire to identify demographics, health status, risk behavior and drug use was administered at baseline and every 6 months, along with blood tests to identify their HCV status. **RESULTS:** A total of 518 subjects were screened (12/07 - 02/09), with 245 (47%) being viremic and 69 (13 %) meeting criteria for inclusion in the study: 18 in the non-infected, 29 in the spontaneous and 22 in the SVR arms respectively. There were no significant differences among the 3 groups with respect to age, ethnicity, source of income, unstable housing, and being on opiate maintenance program. Over 5-18 months follow-up, 20% of the non-infected group became viremic, as compared to 0% of the other two groups (p=0.04). Injecting drugs in past 30 days (p=0.004), sharing non injection equipment (p=0.015), heroin, amphetamines, and combined drugs use was significantly higher in the non-infected arm compared to SVR arm (p=0.02, 0.04 and 0.02 respectively). There were no significant differences in drug use and risk behavior between non-infected and spontaneous arms. **CONCLUSION:** We have now demonstrated in a prospective cohort with systematic follow-up that viremic HCV infection is more likely to occur in those who have never been previously infected, and that this susceptibility to infection cannot be completely explained by an increase in risk behavior, at least as compared to individuals who have cleared their

viremia spontaneously. Whether a decreased rate of viremia following SVR relates to some host-related protective factors or is due to a change in IDU-related risk as a result of engagement in the health care system is currently under study in our centre.

Risk Factors for Primary Hepatocellular Carcinoma in Hospitalized Patients in the United States in 2006. F.Aslinia; C.D.Howell Program Number: 775

BACKGROUND and **AIMS:** The incidence of hepatocellular carcinoma (HCC) in the US has more than doubled during the past 2 decades, with the highest incidence in African Americans and other races compared to White Americans. The aim of the current study was to compare the risk factors for HCC in US racial groups. **METHODS:** We analyzed 4567 HCC cases (ICD-9: 155.00) among African Americans (AA), Asians or Pacific Islanders (AS-PI), Hispanics, Native Americans, Caucasians(CA), and other races in the Nationwide Inpatient Sample (NIS) Database from 2006, a stratified 20% sample of non-federal hospital discharges. The risk factors for HCC were hepatitis C infection (HCV), hepatitis B infection (HBV), alcoholic liver disease (ALD), diabetes mellitus (DM), and cryptogenic cirrhosis. **RESULTS:** The mean age for hospitalized patients with HCC was 63+/-13 years and 74% were male. Compared to CA, AA and Hispanics were significantly younger (Table). Overall, HCV (24%), DM (16%), ALD (9%), HBV (6%) and cryptogenic cirrhosis (5%) were the more common single risk factors for HCC. The most common concurrent risk factors for HCC included ALD and HCV (9%), DM and HCV (7%), HBV and HCV (1.5%), ALD and HBV (0.6%) and ALD, HCV and HBV (0.6%). Compared to CA, HCV was more common in AA and Hispanics; HBV was more common in As-PI and AA; ALD was less common in AS-PI; and DM as the only risk factor and cryptogenic cirrhosis were less common in AA. **CONCLUSION:** HCV was the single most common risk factor for HCC in hospitalized patients in the US in 2006, followed by DM, ALD and HBV with significant variation among racial groups.

A simple strategy to screen for acute HCV infection among newly incarcerated injection drug users. A.Y.Kim^{1,5}; C.E.Birch^{1,3}; E.H.Nagami^{1,3}; et al. Program Number: 777

BACKGROUND: Although injection drug users (IDUs) are at high risk for acute hepatitis C virus (HCV) infection, they are often not identified during this stage because most patients are asymptomatic and do not present to medical care. In a prior pilot study, we demonstrated that HCV infection was the most common cause of acute symptomatic viral hepatitis among inmates presenting for medical care at two sites within the Massachusetts state correctional system. The objective of this study was to evaluate whether risk factor-based screening of newly incarcerated inmates would enhance identification of acute/early HCV cases, including asymptomatic individuals. **METHODS:** A brief questionnaire concerning IDU practices and past testing for HCV was administered during the initial medical evaluation at two intake sites for recently incarcerated male and female inmates. High-risk individuals were further evaluated for evidence of acute/early HCV infection. **RESULTS:** Over a 15-month period, we screened 3,248 inmates for behaviors placing them at risk for newly-acquired HCV infection. We identified 141 high-risk individuals (mean 9.6 individuals/month; range 0-16). After further evaluation, 37 inmates (gender: 13 males, 24 females; race: 32 Caucasian, 4 Hispanic; and one mixed African-American/Caucasian) were diagnosed with acute/early HCV infection. Our case-finding rate for acute/early HCV was 2.5 patients/month, representing a nearly four-fold increase compared to our prior historical control period. Overall, we estimate an incidence of ~1.1% [95% CI 0.8%-1.5%] of acute / early HCV infections among newly incarcerated prisoners within the Massachusetts state prison system. **CONCLUSIONS:** Systematic screening based on risk factors with targeted follow up successfully identifies persons with acute or early HCV in an incarcerated population. The nationwide implementation of this simple strategy could potentially identify more than 7,500 annual cases of acute or early HCV infection in prison-based populations.

Pretreatment prediction of virological response to peginterferon plus ribavirin therapy in patients with chronic hepatitis C using hepatic gene expression profiling. M.Honda; A.Sakai; M.Nakamura; S.Kaneko Program Number: 792

OBJECTIVE: Although pegylated interferon (Peg-IFN) and Ribavirin (RBV) combination therapy has become a popular modality for treating patients with chronic hepatitis C virus (CH-C), about 50% of patients usually relapse. We previously reported that prior up-regulation of interferon stimulated genes (ISGs) in the liver is related to poor treatment outcome. However, the clinical relevance of this finding for pretreatment prediction has not yet been fully evaluated. **MATERIAL AND METHODS:** Eighty-eight patients with CH-C who completed Peg-IFN and RBV combination therapy were enrolled. All patients were infected with genotype 1b HCV with high viral load (>100 IU/ml). The mean age of patients was 55.8 (mean SD), and histological assessments of the fibrosis stage of the liver were distributed as follows: F1=26; F2=26; F3=24 and F4=12. Patients were administered Peg-IFN and RBV combination therapy for 48 weeks. The final outcome of the treatment was assessed 24 weeks after cessation of the combination therapy. Liver biopsies were obtained from all patients before treatment and hepatic gene expression was analyzed using the Affymetrix GeneChip system. **RESULTS:** Forty-one out of 88 patients (47%) achieved sustained viral response (SVR). Hierarchical clustering analysis using 30,757 non-filtered genes clustered patients into two groups, SVR and non-SVR. In the non-SVR group, signaling pathways of JAK-STAT, IFN-gamma and apoptosis were activated compared with the SVR group. We precisely examined the relationship between the expression of 37 representative ISGs in the liver and the amount of HCV-RNA before treatment. Interestingly, in the SVR group, there was a significant negative correlation with ISGs and HCV-RNA ($p < 0.001$), indicating that IFN signaling acts to suppress HCV. No significant correlation was observed in the non-SVR group, indicating the occurrence of IFN resistance in the liver. We calculated the IFN resistant index (IFN-RI) by multiplying 37 standardized ISG expressions by HCV-RNA. Among various clinical parameters, the level of γ -GTP ($p < 0.001$), serum insulin levels ($p = 0.0026$) and HOMA-IRs ($p = 0.0016$) were significantly correlated with IFN-RI. Multivariate logistic regression analysis identified that fibrosis stage (F3-4, odds: 8.77), age (55, odds: 3.49) and IFN-RI (odds range: 5.11-12.4) significantly contribute to the outcome of non-SVR. The area under the curve was 0.88. Discriminate analysis showed that a predictive value for SVR was 88% and for non-SVR was 74%. **CONCLUSION:** Using hepatic ISG expression profiling, we could estimate IFN resistance before treatment, and IFN-RI can be a useful marker for predicting treatment response.

Long term follow - up of chronic hepatitis C patients after interferon based anti - viral therapy. H.Hofer; T.Scherzer; S.Beinhardt; K.Rutter; et al. Program Number:

BACKGROUND and Aim: Antiviral therapy of patients with chronic hepatitis C is aimed to reduce long-term complications like liver cirrhosis, portal hypertension and hepatocellular carcinoma. Persistence of HCV at low levels after therapy induced resolution of chronic hepatitis C has been reported. Aim of the present study was to evaluate clinical outcome of antiviral therapy in a large cohort of chronic hepatitis C patients with emphasize on prevention of long-term complications and durability of HCV eradication in SVR-patients. **PATIENTS and METHODS:** Five hundred and sixty three patients (m=378, f=185; HCV-1: 55.4%, HCV-2: 2.3% HCV-3: 20.1%, HCV-4: 10.8%; 26.3% with pre-treatment cirrhosis) who received antiviral therapy between 1988 and 2006 were regularly followed. Out of this 563 patients 251 patients (m=164, f=87; HCV-1: 50.0%, HCV-2: 4.0%, HCV-3: 27.6%, HCV-4: 12.4%, 26.2% with pre-treatment cirrhosis) with a SVR and a follow up time of >12 months after the end of therapy were evaluated. Twelve patients received monotherapy with standard interferon-alpha, 64 received standard interferon-alpha in combination with ribavirin, one patient received pegylated interferon alone and 174 received pegylated interferon in combination with ribavirin. Serum HCV-RNA was tested by the COBAS AMPLICOR HCV test, v2.0 or COBAS TaqMan HCV test, respectively. **RESULTS:** The median

follow-up duration was 56.0 [12-214] months [range]. All 251 sustained virological responders (100%) with long-term follow-up remained HCV RNA negative during follow up. No late relapses were observed so far. 222/250 (88.8%) patients had transaminases within the normal range. In three patients (1.2%) with SVR a hepatocellular carcinoma was diagnosed during follow up. One additional patient developed decompensated cirrhosis (Child C) 4 years after therapy.

CONCLUSION: No recurrence of HCV infection was observed in any patient with SVR after antiviral therapy and the vast majority of patients with a successful HCV eradication remain free of liver disease after long term follow up. Thus, long-term prognosis of SVR patients (up to 18 years) is promising, although the risk of HCC development and of progressive liver disease is not prevented completely.

Treatment of chronic hepatitis C virus infection in IVDU: long term (4 year) follow up.

J.D.Farley Program Number: 805

BACKGROUND: Treatment of HCV in IDU has been demonstrated to be effective. Previous reports suggest reinfection and relapse in IDU is low. There is little data on the long term follow up of those successfully treated. We encourage regular follow up and monitoring of HCV status of those treated for HCV in our clinic. We previously reported 18 reinfection cases occurring in our patient population (AASLD 2008). As of May 30, 2009 we have 33 confirmed HCV reinfection cases. We now report on the outcome of a 4-year follow up evaluation after successful treatment of HCV in IDU. **METHODS:** Retrospective chart review of HCV patients who were successfully treated (had sustained virologic response) with Pegylated interferon alfa or beta and Ribavirin combination therapy. **RESULTS:** 211 patients were followed up post SVR for a range of six months to four years. Of those, 142 were former IVDU and likely acquired the HCV through IVDU. Of these 211 (38 %) were lost to follow up; 131 (62 %) were regularly monitored post SVR. Of those, 98 (74 %) remained virus free. We identified 33 IDUs who became re-infected post SVR (HCV RNA undetectable at least six months after completing the recommended treatment regimen, and subsequently was detected). Of the 33, a different genotype was identified in 24. Eleven had the same genotype as pre-treatment; unfortunately, more specific analyses were not available to absolutely confirm reinfection. Two relapses were identified. Three cases are still unconfirmed and being evaluated. There was one spontaneous clearance after reinfection. The time to occurrence of re-infection had a mean of 77.7 weeks after the scheduled EOT. The primary attributable causes of reinfection included intravenous drug use (76 %), tattooing (21 %) and direct blood contact (3 %) from a fight involving significant blood splash. **CONCLUSION** Our findings show that unlike earlier reports, the possibility of hepatitis C reinfection is significant among IVDU. We feel this is explained because our period of observation has been much longer (four years) than those reported. Also, we routinely follow up IDUs treated for HCV. We ask regarding continued high risk IV drug use activity after treatment and test for possible relapse or reinfection every six months. We note that there is continued high risk activity after HCV treatment in many. We are trying to ascertain whether factors such as methadone use or other substitution therapies correlate with reinfection. We feel that more monitoring (clinical and laboratory) should be emphasized for IDUs including regentyping of those had the HCVRNA detected.

Combination antiviral therapy for chronic hepatitis C in illicit drug users: meta - analysis of prospective studies. B.Zanini¹; L.Covolo²; F.Donato²; A.Lanzini¹ Program Number: 813

AIM: According to most recent international guidelines, ongoing illicit drug use is no longer regarded as a contraindication to antiviral therapy for Chronic Hepatitis C (CHC); nevertheless in clinical practice only few IDUs access specific treatment for hepatitis C virus because of prejudice of poor adherence and of lack of treatment efficacy. The aim of our meta-analysis was to assess efficacy and safety of combination therapy of recombinant or pegylated interferon alpha plus ribavirin in the treatment of CHC in IDUs. **METHODS:** We performed a sensitive search of three electronic

bibliographic databases (Medline, Embase and the Cochrane Library) and a hand-searching revision of abstract-books from five international liver meetings for papers and abstracts that met pre-defined search criteria. Search term used were "hepatitis C" or "HCV" or "peginterferon" or "interferon" or "antiviral therapy" AND "methadone" or "IDUs". Data for meta-analysis were collected according to QUORUM (Quality of Reporting Meta-analyses) statement guidelines. For inclusion into the meta-analysis, the studies had to meet the following criteria: (1) sample size over 15 patients, (2) clear definition of antiviral schedule for type, dose and duration of treatment, (3) uniform combination antiviral therapy for the whole study population. **RESULTS:** Out of 95 papers and abstracts, 13 prospective studies were included (3 case-control, 2 randomised and 8 observational in study design) and information on a cohort of 582 IDUs was analysed. The estimated overall Sustained Virologic Response (SVR) was 53% (41-65%, CI) and was similar to the SVR rate reported in registration trials of treatment of CHC that excluded IDUs from the study population: 50% (39-61%, CI). Among IDUs drop out and psychiatric severe adverse events leading to treatment discontinuation rates were 24% (18-29%, CI) and 4% (1-7%, CI) respectively. Such prevalences were similar to those reported in registration trials excluding IDUs in selection criteria: 26% (12-41%, CI) and 2% (0-6%, CI) respectively. Active ongoing drug use negatively affects rate of SVR (40%), while programs of management involving a multidisciplinary team and careful assessment of the psychiatric status of patients before and during treatment improve response rate (55% and 76%, respectively). **CONCLUSION:** Antiviral treatment for chronic hepatitis C in IDUs is effective and safe in clinical practice. Patients abstinence and multidisciplinary approach enhance treatment efficacy.

Discordance between HCV RNA week 24 test RESULTS of three different HCV RNA assays during treatment of chronic hepatitis C: optimization of treatment length using the most sensitive HCV RNA assay. R.Roomer; A.Heijens; M.Schutten; H.L.Janssen; R.J.de Kneeg
Program Number: 827

BACKGROUND and AIMS: The development of new, more sensitive HCV RNA assays may necessitate re-evaluation of stopping rules, e.g. HCV RNA negativity at week 24 during treatment with peginterferon alfa and ribavirin (PEG-IFN/RBV) for chronic hepatitis C. The aim of this study was to assess the concordance between week 24 HCV RNA test results of COBAS AMPLIPREP/COBAS TaqMan HCV test (limit of detection [LOD] <15IU/mL), COBAS AMPLIPREP HCV TEST V2.0 (LOD <20 IU/mL) and VERSANT TMA HCV RNA qualitative assay (LOD <5IU/mL). **METHODS:** From a cohort of 321 patients treated with PEG-IFN/RBV between 2000 and 2009 43 patients with genotype 1 or 4 and detectable HCV RNA at week 4 or 12 but with undetectable HCV RNA at week 24 tested with the COBAS AMPLIPREP HCV TEST V2.0 were selected. Week 24 HCV RNA samples of selected patients were retested with the COBAS AMPLIPREP/ COBAS TaqMan™ and the VERSANT TMA HCV qualitative assay to investigate discordance between tests results. **RESULTS:** Thirty-seven patients had genotype 1 and 6 had genotype 4. All patients had detectable HCV RNA at week 4, and 9 patients had quantifiable HCV RNA at week 12, range 620-12300 IU/mL. Nineteen of 43 patients (44%) achieved SVR. Four of 9 patients with quantifiable HCV RNA at week 12 achieved SVR. Viral breakthrough occurred in 4 patients and 20 patients relapsed. All 43 samples from week 24 were re-tested with COBAS AMPLIPREP / COBAS TaqMan™ (cut off HCV RNA <15 IU/mL) were HCV RNA negative. Six of 43 samples (14%) retested with the much more sensitive VERSANT TMA HCV RNA qualitative assay (LOD 5 IU/mL) were HCV RNA positive. None of these patients achieved SVR. **CONCLUSION:** Discordance was found between VERSANT TMA HCV RNA qualitative assay and the other less sensitive assays. In this study a proportion of patients were treated unnecessarily because of the use of less sensitive HCV RNA assays at week 24 during HCV treatment. According to these data, at week 24 the most sensitive HCV RNA assay should be used.

Efficacy of Tailored Extension of Pegylated - Interferon and Ribavirin in Chronic Hepatitis C Patients. H.Ikeda¹; M.Suzuki¹; N.Yamada^{1,3}; et al. Program Number: 836

BACKGROUND: We tailored extended treatments using pegylated interferon (PEG-IFN) and ribavirin (RBV) to viral responses after initiation of therapy for Japanese Genotype 1b chronic hepatitis C patients. The aim of this study was to prospectively investigate the efficacy and safety of extended treatment based on the week when HCV-RNA became undetectable. In addition, we investigated predictive factors of SVR and NR including viral genetic factors. **METHODS:** Total of 201 Genotype1b CHC patients (male 108, female 73, mean age 55.3 years) were enrolled in this study from July 2005 to August 2007. Patients received peginterferon alfa-2b (1.5g/kg/wk) and ribavirin (600-1200mg/day). Patients received treatment for an individualized duration based on the week when HCV RNA first became undetected by COBAS Amplicor monitor HCV v.2.0 (Roche). [1] Week4; rapid viral response (RVR); 48 weeks duration. [2] Week8; early viral response (EVR); 52 weeks duration. [3] Week12; EVR; 60 weeks duration. [4] Week16-24; late viral response (LVR); 72 weeks duration. Patients viremic at Week24 were assigned to NR and excluded from this study. All patients were followed up for further 24weeks, and we investigated SVR rate of these groups.

RESULTS: Treatment course was completed in 167 of the 201 patients (83.1%). The percentage of patients who achieved RVR, EVR and LVR patients were 11.0%, 40.3% and 18.9%, respectively. Overall SVR rate was 52.2%. SVR rates for RVR, EVR and LVR were 95.7% (22/23), 77.5% (62/81) and 55.3% (21/38), respectively. In multivariate analysis, the independent predict factors of SVR were age (>60 years, OR 0.31, 95%CI 0.13-0.72, p<0.01), platelet count (>13x10⁹/L, OR 3.34, 95%CI 1.37-8.15, p<0.01), viral load (>2x10⁶IU/ml, OR 0.17, 95%CI 0.07-0.41, p<0.01), amino acid substitution at ISDR (Mutant type, OR 3.36, 95%CI 1.16-11.3, p=0.03) and amino acid substitution at 70 at HCV core region (wild type, OR 4.14, 95%CI 1.73-9.90, p<0.01). The independent predict factors of NR were platelet count (>13x10⁹/L, OR 0.32, 95%CI 0.14-0.76, p<0.01) and amino acid substitution at 70 at HCV core region (wild type, OR 0.18, 95%CI 0.08-0.41, p<0.01). In LVR patients, there is no pretreatment predictive factor of SVR, but dose reduction of RBV was the only predictive factor of SVR in univariate analysis (OR 0.14, 95%CI 0.03-0.72, p=0.03). **CONCLUSION:** Extended treatment of PEG-IFN plus RBV based on the week when HCV RNA became undetected is effective strategy for genotype1b CHC patients. Amino acid substitutions at ISDR and 70 in HCV core region were predictive factors of SVR. It is preferable to avoid dose reduction of RBV in LVR patients to reduce relapse rate.

Evaluation of HCV RNA decay 48 hours after starting combination therapy with Pegylated Interferon and Ribavirin as a tool for early prediction of Sustained Virologic Response.

G.Parruti¹; F.Sozio¹; A.Pieri¹; E.Pollilli²; et al. Program Number: 838

Pegylated Interferons (PEG-IFNs) in combination with Ribavirin (RBV) significantly improved the chances of HCV eradication in patients infected with HCV. Furthermore, evidence of better Sustained Virological Response (SVR) rates in early responders drew attention on the timing of virologic response to predict SVR. Data on a rapid HCV-RNA decay after IFN administration suggested us in 2000 to investigate whether a Very Rapid Virologic Response (VRVR) could effectively predict SVR in the era of PEG-IFNs. Between 2000 and 2006, we consecutively enrolled every consenting patient starting PEG-IFN/RBV therapy at our Institution for HCV-RNA evaluation 48 hours after starting therapy. We also evaluated sex, age, BMI, HCV genotype, liver histology, AST, ALT and HCV RNA levels at baseline, previous IFN exposure, PEG-IFN type, dose reductions, adverse events, HBV and HIV coinfections, markers of autoimmunity, early virologic response (EVR) and VRVR as predictors of SVR. VRVR was categorized as a drop in HCV RNA >80% from baseline. Consent was provided by 171 patients. Of these, 19 missed their 48h date; for 14 additional patients, assays for qualitative HCV RNA only were performed; 8

subjects were lost at follow up. As a consequence, 130 patients were evaluable for final analyses. Males were 68%, mean age 42.8 y; 9% were coinfecting with HIV. Drug addicts were 52%; 80% of patients were IFN nave; 48.5% had HCV genotype 1. Mean HCV viremia at baseline was 601.000 IU/mL. One third of patients had severe liver histology (F3, Knodell); 43% of patients had ALT levels 2.5 UNL; 56% was prescribed PEG IFN alfa2b, according to physician's choice; 78% were treated before 2005. One third of patients took 80% of prescribed doses. SVR was obtained by 65% of patients; cEVR by 78% of patient, 83% of whom achieved SVR. VRVR was reached by 77% of patients and 75% of these achieved SVR. Univariate analyses of SVR predictors confirmed the role of HCV genotype, liver histology, previous exposure to IFN and dose reduction <80%. In logistic multivariate analyses evaluating age, sex, genotype, nave status, dose reduction, type of IFN and VRVR, VRVR turned out to be the most powerful predictor of SVR (OR 5.03; CI 1.67-15.09). **Our study confirms** on the field the efficacy of PEG-INF-based regimens in recent years, as well as the role of age, genotype, HIV-coinfection, liver histology and previous exposure to IFN as "a priori" predictors of SVR. VRVR and ERV were approximately as powerful in predicting SVR independently of genotype. VRVR may therefore be a useful tool in clinical practice, to decide whether to treat or not particularly frail patients.

Age 45 years or younger is strongly associated with antiviral treatment response in hepatitis C virus infected patients. H.Nanna¹; N.Obel²; J.Bukh^{3,4}; N.Weis^{1,4} Program Number: 877

BACKGROUND: Previous studies on predictors of sustained virologic response (SVR) in chronic hepatitis C virus (HCV) infected patients treated with peginterferon and ribavirin, included patients in clinical trials, a highly selected group, or patients treated outside of clinical trials. The aim of the present study was to estimate baseline predictors of SVR in patients treated with peginterferon and ribavirin from 2002-2007. **METHODS:** All HCV infected patients treated with peginterferon and ribavirin between 1 January 2002 and 1 January 2007 in 9 different Danish Hospitals were included in the study. Patients with positive HIV-antibody test or HBsAg test were excluded. Both patients treated in clinical trials, and patients treated in routine medical settings, were included in the study. We calculated predictors of sustained virologic response (SVR) using univariate and multivariate regression analyses. **RESULTS:** In all, 356 patients were included in the study, 115 (32%) with genotype 1-, 232 (65%) with genotype 2- or 3-, and 9 (3%) with genotype 4 infection. SVR rates were 45%, 70%, and 67% for genotypes 1, 2/3, and 4 respectively. Median age was 46 years (range 21-71). In multivariate regression analyses genotype 2/3 (genotype 2/3 vs. 1; OR= 2.18, 95% CI: 1.27-3.76), age 45 years (> vs. 45 years; OR= 0.56, 95% CI: 0.32-0.92), and HCV-RNA level 600.000 IU/mL at treatment initiation (> vs. 600.000 IU/mL; OR=0.56, 95% CI: 0.33-0.95) were significant predictors of SVR. However, in patients 45 years, genotype and HCV-RNA level were no longer significant predictors of SVR (OR=1.51, 95% CI: 0.54-4.23, and OR=0.62, 95% CI: 0.24-1.61 respectively). Age and HCV-RNA level remained significant predictors of SVR in genotype 1 infected patients (OR= 0.26, 95% CI: 0.07-0.96, and OR = 0.25, 95% CI: 0.08-0.83). The SVR rate, in patients 45 years with genotype 1 was similar to SVR rates for patients with genotype 2/3 and age > 45 years (63% and 65% respectively), and almost twice the rate of SVR for genotype 1 infected patients aged > 45 years (36%). For all subgroups, SVR was significantly lower, if treatment had been stopped before planned. **CONCLUSION:** The difference in SVR rates between those 45 years and those >45 respectively, was so significant, that one could consider whether treatment for HCV infection (especially for genotype 1 patients) should be initiated as early as possible, despite of clinical findings of little or no liver disease.

Short - term peginterferon - - 2a monotherapy for chronic hepatitis C patients with low HCV RNA load and immediate virological response. M.Yada; N.Yamashita; K.Motomura; T.Koyanagi; S.Sakamoto; A.Masumoto Program Number: 878

It is important to design optimal regimens in interferon (IFN) therapy for chronic hepatitis C. The treatment duration could be shortened in patients who achieve hepatitis C virus (HCV) RNA negativity in serum at an early stage of the therapy. Focusing on the initial virological response to IFN administration, we studied the efficacy of short-term PEG-IFN- monotherapy for patients who had low pretreatment HCV RNA load. Defining the "immediate virological response (IVR)" as loss of HCV RNA in the serum after the first administration of PEG-IFN-, we then conducted a 12-week course of PEG-IFN--2a monotherapy for 38 patients who exhibited IVR. Based on the intention-to-treat analysis, 35 patients (92.1%) achieved sustained virological response. One patient (2.6%) relapsed with HCV RNA in the serum 12 weeks after the end of treatment. Two patients (5.3%) withdrew from the study during the 24 week follow-up period. Short-term PEG-IFN--2a monotherapy is highly effective for chronic hepatitis C patients, who have low pretreatment HCV RNA load and show IVR.

Treatment compliance in patients taking RibaPak or ribavirin 200mg: Final analyses from the ADHERE registry. V.K.Rustgi^{1,2}; I.Alam³; B.Cecil⁴; et al. Program Number: 880

BACKGROUND: Poor compliance to Hepatitis C virus (HCV) treatment is an important cause of treatment failure. Traditional ribavirin 200 mg (RBV) treatment is associated with a significant daily pill burden (up to 7 a day). RibaPak (RBP) is available as 400mg and 600mg ribavirin tablets and offers simplified dosing at 2 pills a day. This study examined whether improved compliance was associated with RBP vs. RBV. **METHODS:** Accurate Dosing in Hepatitis C: Examining the RibaPak Experience (ADHERE) was a U.S., 24 week, multi-center, prospective, observational registry capturing data on compliance with RBP vs. RBV in adults with HCV; all subjects also received pegylated interferon. Compliance was measured by the proportion of subjects remaining on treatment over 24 weeks and, for those who remained on treatment, by pill counts at treatment weeks 0-4, 8-12 and 20-24. **RESULTS:** 503 patients (RBP = 346, RBV = 157) from 38 sites were included. Demographic characteristics, baseline mean viral load, and median drug dose prescribed (1000 mg) were similar between the groups. Subjects' mean age was 48.5 years; 54% were men and the majority (71%) were Caucasian. A greater proportion of RBV subjects prematurely discontinued treatment compared to RBP subjects. While there was a significantly ($P < 0.04$) greater proportion of RBP subjects remaining on treatment at both weeks 12 and 24, the greatest discrepancy in discontinuation rate was between 5 and 12 weeks where there was a 49% difference in the proportion of RBV (15.9%) vs. RBP (8.1%) subjects that discontinued. Furthermore, subjects who discontinued between 5 and 12 weeks missed a significantly ($p = 0.002$) greater mean number of doses (8.9) during the 0 to 4 week treatment period vs. subjects who completed 12 weeks (2.5), suggesting that early non-compliance is associated with later discontinuation. For patients who remained on treatment, the median mg taken per day was significantly ($p = 0.01$) greater for RBP (1200) vs. RBV (1000) at 12 weeks. **CONCLUSIONS:** These data demonstrate higher compliance for RBP vs. RBV. The discontinuation rate was greater for RBV, and RBP was associated with greater milligrams of drug taken in the group that did not discontinue. Importantly, no defining characteristics were apparent to determine patients at high risk for treatment discontinuation; these data suggest first line treatment with RBP offers the best prospect for less discontinuation and improved treatment compliance. The cumulative impact of treatment discontinuation has the potential to impact SVR, quality of life, and healthcare costs.

Determinants of Engagement in Care of Inner City HCV - Infected Injection Drug Users (IDUs). B.Conway¹; H.Tossonian¹; J.Grebely²; Program Number: 887

OBJECTIVES: The majority of prevalent and incident cases of HCV infection in Canada occur in current and former IDUs. There is an urgent need to better characterize this population in terms of its demographics, knowledge base about their disease and willingness to enter into treatment, to

better plan for the deployment of health care resources to accommodate their needs. We conducted a prospective survey of attendees of four inner city British Columbia clinics to address these issues. **METHODS:** HCV-infected patients attending inner city clinics in Vancouver, Nanaimo and Victoria were identified for inclusion. Selected demographic information was collected, along with information about previous or current consideration for HCV treatment, as well as reasons for having ever sought or been offered treatment, or having refused (or been refused) treatment if considered. **RESULTS:** A total of 296 patients (64% male, 21% First Nations, median age 46) were included. Key baseline characteristics included: Unstable housing (65%), active IDU (55%) and opiate substitution (55%). Of those not having sought treatment (n = 195), the main reasons were: lack of information about treatment (27%), absence of symptoms (17%), perceived treatment toxicity (8%) and unstable drug use (7%). Of 108 individuals not accepting treatment once offered, the main reasons were concerns about side effects (16%), lack of interest (12%), absence of symptoms (10%) and unstable drug use (7%). Up to now, 34 patients have been treated, with the main reasons for exclusion from treatment being lack of interest (51%), genotype 1 or 4 requiring longer treatment (24%) and lack of reimbursement of medications (9%). **CONCLUSION:** Lack of interest and information along with unstable drug use appear to be the main drivers limiting the uptake of HCV treatment in our inner cities. The establishment of peer-driven discussion groups led by HCV clinical and research staff will play an important role in making treatment more accessible, especially when delivered in concert with addiction treatment services, and with specific protocols to address treatment toxicities in a proactive manner.

Treatment of recent hepatitis C virus infection in a predominantly injection drug user cohort: the ATAHc Study. G.J.Dore¹; M.Hellard²; G.Matthews¹; et al. Program Number: 888
Treatment of acute hepatitis C virus (HCV) infection produces high sustained virological response (SVR) rates, but few studies have examined outcomes among injecting drug users (IDUs). We evaluated the efficacy of treatment of recent HCV infection (acute and early chronic HCV), within a predominantly IDU-acquired HCV population. The Australian Trial in Acute Hepatitis C (ATAHC) was a prospective study of the natural history and treatment of recent HCV infection. Participants were eligible if they were within 6 months of their first anti-HCV antibody positive result and had a documented anti-HCV seroconversion within 24 months, or acute clinical HCV within the past 12 months. HCV participants received PEG-IFN alfa-2a (180 g/week, n=74) and HCV/HIV co-infected participants received PEG-IFN alfa-2a (180 g/week) with ribavirin (n=35) for 24 weeks. Between June 2004 and February 2008, 167 participants with recent HCV infection were enrolled (79% had injected in the previous 6 months). Among 74 HCV participants receiving PEG-IFN alfa-2a, the SVR was 55% overall and 72% among adherent participants (n=50). In multivariate analyses, baseline factors associated with reduced SVR included decreased social functioning and current opiate pharmacotherapy. Among 35 HCV/HIV participants receiving PEG-IFN alfa-2a/ribavirin, the SVR was 74% overall and 75% among adherent participants (n=32). Among all adherent participants (n=82), there were 11 non-responders, 1 viral breakthrough and 8 viral relapses. Treatment of recent HCV among adherent IDUs including those with HIV co-infection is effective. Strategies to enhance adherence among IDUs with recent HCV infection should improve treatment outcomes.

Reduced liver fibrosis: Coffee or caffeine? A.A.Modi¹; J.J.Feld²; Y.Park¹; et al. Program Number: 1097

INTRODUCTION: Higher caffeine consumption has been shown to be associated with lower risk of elevated ALT levels, reduced fibrosis as well as all-cause mortality in pts with chronic liver diseases (CLD). However, it is not clear if the protective effect is due to caffeine or coffee. **Aim:** To determine whether higher caffeine intake from coffee or from other sources is associated with decreased severity of fibrosis in pts with CLD. **METHODS:** A questionnaire aimed at

assessing the frequency of consumption of caffeine-containing foods and beverages, including soft drinks, coffee, tea, cocoa as well as caffeine-fortified drinks, chocolate bars, caffeine-containing medications and alcohol intake was administered to all patients undergoing liver biopsy. Caffeine consumption was quantified as the average mg of caffeine per day in which one 8 oz cup of coffee = 137 mg. Liver histology was scored using a modified Ishak scoring system for activity and fibrosis. Logistic regression was performed to evaluate the association of caffeine & coffee with advanced liver fibrosis (Ishak score³). **RESULTS:** Among the 177 pts (56% male, 59% Caucasian, mean age 51 years), 121 had HCV, 19 HBV, 3 HDV, 17 NASH, 4 PBC and 4 AIH. 30% had advanced fibrosis. The average caffeine intake was 195 mg/day (~ 1.5 cups of coffee/day). Among the entire cohort, after adjusting for other factors known to be associated with fibrosis (age, sex, race alcohol intake and baseline ALT), caffeine intake 308 mg/day (~2.2 cups of coffee daily) was associated with reduced fibrosis compared to lesser amounts or no caffeine intake (OR=0.19, 95% CI 0.05-0.64, p=0.008). Caffeine consumption from sources other than coffee (caffeinated cola, green or black tea) was not associated with reduced liver fibrosis in the population as a whole (OR per 67 mg of caffeine 0.84, 95% CI: 0.60-1.17, p=0.30) or in those with HCV infection (OR per 67 mg of caffeine 0.78, 95% CI: 0.52-1.16, p=0.21). The mean consumption of caffeine restricted to coffee consumption was 152209 mg/day with a 75th percentile of 270 mg/day. For all patients consuming greater than this amount, the multivariate adjusted odds ratio of advanced liver disease was 0.39 (95% CI: 0.15-0.99, p=0.049) and 0.26 (95% CI: 0.07-0.89, p=0.032) for patients with HCV. After controlling for other factors, consumption of >2 cups of coffee daily was associated with lower odds of advanced fibrosis (OR 0.29, 95% CI: 0.09-0.92, p=0.036) **CONCLUSION:** Caffeinated coffee, but not other sources of caffeine, is associated with reduced liver fibrosis.

HCV Infection is Associated with High Comorbidity Burden in Europe. H.F.Zhang¹; D.Mills²; S.Wagner²; D.Freedman² Program Number: 1340

BACKGROUND: Hepatic impairment from chronic hepatitis C (CHC) has significant implications for drugs that are extensively cleared by liver, which presents extra challenges to manage comorbidities for CHC patients. The purpose of this study is to assess the comorbidity burden of hepatitis c virus (HCV) infection in Europe to better understand the needs for proper disease management of patients with CHC. Method: National Health and Wellness Survey (NHWS) data were applied when CHC data were collected from 2006 to 2008 in France, Germany, Italy, Spain, and UK. NHWS is an annual cross-sectional survey from a random representative adult population, including information regarding healthcare attitudes, behaviors, demographic and disease characteristics, resource utilization, and health-related outcomes. Those with self-reported CHC were categorized as cases. Propensity-matched non-CHC survey responders were selected as controls based on country, gender, age, education, employment, and year of survey. Conditional logistic regression was applied controlling for HIV, marital status, smoking status, alcohol consumption and body mass index. **RESULTS:** The final sample included 864 cases and 864 closely matched controls. 61% were male with mean age of 49.8 in final sample. After adjusting for HIV status, the most prevalent conditions ever experienced by CHC patients included hypertension (27%), high cholesterol (17%), diabetes (12%), chronic bronchitis (11%), arthritis (10%), hepatitis B (10%), thyroid disorders (10%), cancer (9%), and ulcer (gastric or duodenal - 9%). Compared to the control adjusting for HIV status and other covariates, CHC patients were associated with significantly higher risks for 32 medical conditions collected in the survey, including hepatitis B, diabetes, hypertension, heart attack, chronic kidney disease, moderate/severe renal disease, COPD, depression, anxiety, panic disorder, and insomnia, etc.. Most of these conditions require long-term or intensive pharmacological management. Normal liver function is essential for many of these treatments to be tolerable, effective, or both. **CONCLUSIONS:** CHC patients have a high burden of comorbidities. Treating HCV infection early to prevent the deterioration in liver function is

essential for the management of comorbid conditions, and should be among the key goals of comprehensive CHC management strategies.

Menopause is Associated with Increased HCV RNA Level in Patients with Chronic Hepatitis C, C.Stern¹; R.Moucarri¹; M.Martinot-Peignoux¹; T.Asselah¹; et al. Program Number: 1413

BACKGROUND/AIMS: High HCV RNA levels have been associated with poor response to antiviral therapy. Female patients with chronic hepatitis C (CHC) have a higher response rate to therapy. Estrogen exposition appears to influence the clinical course of CHC. We evaluated the impact of gender, age, menopause and other factors on HCV RNA levels. **METHODS:** A total of 524 consecutive CHC patients with no prior antiviral treatment and without other causes of liver disease were submitted to a liver biopsy and were eligible for this study. All data were collected at the moment of the liver biopsy. High HCV RNA level was defined as higher than 400,000 IU/mL. HCV RNA levels were analyzed according to clinical, biochemical, virological and histological data. **RESULTS:** The 524 patients presented the following characteristics: male gender 56%, mean age 48.11, mean BMI 25.4, genotype 1 in 55%, median HCV RNA 474,160 IU/mL (519-7,692,000), METAVIR Activity 2 in 27%, Fibrosis 2 in 51% and marked steatosis (>30%) in 30%. High HCV RNA was related to age ($p=0.013$), GGT levels ($p=0.005$), glucose ($p=0.004$), genotype ($p<0.001$) and steatosis ($p=0.013$). In the logistic regression, age >45 years ($p=0.031$), high GGT levels ($p=0.017$) and genotype 1 ($p<0.001$) were independently related to high HCV RNA level. When we analyzed female patients, HCV RNA levels were associated with age (median HCV RNA 237,780 IU/mL under 45 years vs 512,000 IU/mL above 45 years, $p=0.004$), menopause ($p=0.005$), abnormal ALT ($p=0.043$), abnormal GGT ($p=0.013$), glucose levels ($p=0.049$), necro-inflammatory activity 2 ($p=0.019$) and fibrosis 2 ($p=0.039$). In the logistic regression, menopause ($p=0.019$) and GGT levels ($p=0.018$) were the factors associated with high HCV RNA. In contrast, in males, no relation was found between age and HCV RNA levels ($p=0.26$), but genotype ($p<0.001$) and GGT levels ($p=0.026$) were independently associated with HCV RNA levels in the logistic regression. When we compared female and male patients, under 45 years, female patients had lower HCV RNA levels than males ($p=0.02$), but this difference was not observed in patients above 45 years ($p=0.59$). **CONCLUSION:** High HCV RNA levels are associated with older age, genotype 1 and high GGT levels. Age has an impact on HCV RNA levels in female, but not in male patients. This result suggests a possible role of hormones on HCV replication.

SVR RESULTS in Chronic Hepatitis C Genotype 1 Patients Dosed with SCH 900518 and Peginterferon Alfa - 2b for 2 Weeks, Followed by Peginterferon Alfa - 2b and Ribavirin for 24/48 Weeks: An Interim Analysis. J.de Bruijne¹; J.F.Bergmann²; C.J.Weegink¹; et al. Program Number: 1555

BACKGROUND: SCH 900518, a second generation hepatitis C virus (HCV) NS3 serine protease inhibitor, resulted in robust reductions of HCV RNA after 1 week of monotherapy and after 2 weeks of combination therapy with peginterferon alfa-2b (Peg-IFN) with or without ritonavir. At the end of this proof-of-concept (POC) study (i.e. after SCH 900518), all patients were offered standard of care (SOC) with Peg-IFN and ribavirin (RBV). **METHODS:** Forty HCV genotype 1-infected patients (20 treatment-naïve and 20 treatment-experienced) completed the POC study of SCH 900518. These patients received SCH 900518 ($n=32$) or placebo ($n=8$) in combination with Peg-IFN for 2 consecutive weeks, immediately followed by SOC with once weekly 1.5 g/kg Peg-IFN and daily weight-based RBV (800-1400 mg). Patients were treated for 24 or 48 weeks, provided standard stopping rules did not require premature discontinuation. HCV RNA measurements were centrally performed using Cobas Ampliprep/Cobas TaqMan HCV Test (LLD 15 IU/ml). Patients with plasma viral load >1000 IU/mL at start of SOC were analyzed for known resistant mutations by sequence analysis. **RESULTS:** All 40 patients began treatment with SOC (see table), 39 patients

have completed follow-up and 1 patient (placebo) is still in follow-up. Premature discontinuation due to an increase of HCV RNA during SOC ($>1 \log_{10}$ from nadir) was seen in 10 patients who received SCH 900518 (treatment-naïve $n=3$ vs. treatment-experienced $n=7$) and in 1 patient who received placebo. Non-response at week 4, 12 or 24 was seen in 5 treatment-experienced patients (SCH 900518 $n=2$, placebo $n=3$). Virological relapse after SOC was observed in 2 treatment-experienced patients (SCH 900518 $n=1$ and placebo $n=1$). In total 15 patients had HCV RNA >1000 IU/mL at start of SOC; 7 patients received SCH 900518 and 8 patients received placebo. In 5 of 7 SCH 900518 dosed patients at least one of the following variants, associated with protease inhibitor resistance, within the NS3 protease were detected: R155K ($n=5$), A156T/S ($n=2$), V36M/L ($n=4$). **CONCLUSION:** This study demonstrates that administration of SCH 900518 for two weeks (with or without ritonavir) plus Peg-IFN followed by SOC for 24 weeks or 48 weeks resulted in 81% and 38% SVR in treatment-naïve and experienced patients, respectively. These results support further development of SCH 900518 in both treatment-naïve and treatment-experienced patients.

Standard versus high dose ribavirin in combination with peginterferon alfa - 2a (40KD) in genotype 1 (G1) HCV patients coinfectd with HIV: Final RESULTS of the PARADIGM study. M.Rodriguez-Torres¹; J.Slim²; L.Bhatti³; et al. Program Number: 1561

BACKGROUND: HCV patients co-infected with HIV achieve lower rates of sustained virologic response (SVR) compared to HCV mono-infected patients. The standard treatment for HIV-HCV coinfectd patients is peginterferon alfa-2a (40KD) (180 g/wk) plus ribavirin (RBV) at a dose of 800 mg/day (irrespective of genotype) for 48 wks. The PARADIGM study compared standard dose RBV (800 mg/day) to higher dose RBV (1000/1200 mg/day) in patients coinfectd with HIV and G1 HCV. **METHODS:** Adult patients coinfectd with HIV-HCV (G1) were randomized (1:2) to 48 wks of 180 g/wk peginterferon alfa-2a (40KD) plus RBV either at a dose of 800 mg/day or 1000/1200 mg/day. The primary efficacy endpoint was SVR defined as an undetectable HCV RNA (<20 IU/mL) 24 wks after an untreated follow-up period. Secondary efficacy endpoints included RVR (HCV RNA <20 IU/mL by wk 4) and cEVR (non-RVR but HCV RNA <20 IU/mL by wk 12). Hematological growth factors were permitted at the discretion of the physician. **RESULTS:** Overall 410 patients were randomized and treated. Key baseline characteristics and on-treatment outcome are described in the table. Rates of SVR were similar in the standard dose RBV arm compared to the higher dose RBV arm (19% versus 22%, Odds Ratio 1.15, 95% CI 0.68-1.93; $p=0.6119$). **CONCLUSIONS:** Overall rates of SVR were similar for standard and high dose RBV. Patients with an RVR or cEVR had a high chance of achieving an SVR irrespective of the dose of RBV. In HCV-HIV coinfectd patients standard (800 mg/day) and high dose RBV (1000/1200 mg/day) were similarly tolerated with the same proportion of patients (12%) discontinuing for safety reasons. The high drop-out rate for non-safety/efficacy reasons warrants further investigation.

Telaprevir, Peginterferon Alfa - 2a and Ribavirin Improved Rates of Sustained Virologic Response (SVR) in "Difficult - to - Cure" Patients with Chronic Hepatitis C (CHC) : a Pooled Analysis From the PROVE1 and PROVE2 Trials. G.T.Everson¹; G.M.Dusheiko²; P.Ferenc³; et al. Program Number: 1565

BACKGROUND: PROVE1 and PROVE2 are published Phase 2b randomized controlled studies that evaluated the safety and efficacy of telaprevir, peginterferon alfa-2a and ribavirin (T/PR) in treatment-naïve patients with genotype 1 hepatitis C as compared to standard care (PR). The primary aim of this subgroup analysis was to determine whether T/PR could improve sustained viral response (SVR) in subgroups of patients with characteristics that are associated with low virologic response to PR. **METHODS:** Two identical treatment regimens arms were pooled from PROVE1 and PROVE2: 12 weeks of T with 24 weeks of PR (T12/PR24) and 48 weeks of PR (PR48, controls). The following factors potentially having an effect on the SVR rate were evaluated: baseline

HCV RNA level (<800,000 IU/mL vs. 800,000 IU/mL), race (black vs. white), age (45 years vs. >45 years), sex, body mass index (< 25 kg/m² vs. 25 kg/m²), genotype subtype (1a vs. 1b), and liver fibrosis stage (bridging vs. any other). Patients with cirrhosis were excluded from these trials. **RESULTS:** Overall SVR rates were 65% for the pooled T12/PR24 arm and 44% for the pooled PR48 arm (P=0.0001). RVR and SVR rates are shown in the table. By logistic regression analysis, treatment group, baseline HCV RNA level, age group and race were predictors of SVR. Adverse events (T12/PR24 vs PR48) included fatigue (54% vs. 46%), rash (54% vs. 32%), nausea (51% vs. 32%), flu-like symptoms (47% vs. 44%), headache (41% vs. 50%) and pruritus (24% vs. 48%). The incidence of severe rash was 8% in the pooled T12/PR24 arm and 1% in the pooled PR48 arm. The incidence of anemia was 32% in the pooled T12/PR24 arm and 22% in the pooled PR48 arm. **CONCLUSIONS:** Telaprevir-based triple therapy improved SVR rates in patients predicted to have low virologic response to the current standard treatment.

Pegylated interferon alfa - 2a vs pegylated interferon alfa - 2b, plus ribavirin, for chronic hepatitis C genotype 4 patients: a randomized controlled trial. S.Kamal^{2,1}; D.Ghoraba²; L.Nabegh²; et al. Program Number: 1566

BACKGROUND/Objectives: Treatment of chronic hepatitis C virus (HCV) genotype 4 infection has not been yet optimized. This study was designed to compare the safety, efficacy and therapy duration of peginterferon (PEG-IFN) alfa-2a vs PEG-IFN alpha-2b plus ribavirin in chronic HCV genotype 4 patients. Study design/ **METHODS:** In this head-to-head, randomized, double blind clinical trial, patients with proven chronic hepatitis C genotype 4 were randomized to either peginterferon alfa-2a (180 mug/week) or peginterferon alfa-2b (1.5 microg/kg/week) plus ribavirin 1000/1200 mg/day. HCV-RNA was assessed at baseline, weeks 1,2,4,12,24, end of treatment (EOT) and 24 weeks after therapy. Liver biopsies with grading and staging assessment (Ishak score) were performed before therapy in all patients and at end of follow-up to a subset of patients. Patients achieving rapid virologic response (RVR) and complete end of treatment response (cEVR) were treated for 24 and 36 weeks respectively. Patients with partial end of treatment response (pEVR) or slow responders (undetectable HCV RNA after 24 weeks) were treated for 48 and 72 weeks respectively. The primary end point is sustained virologic response (SVR). Comparison of adverse events and quality of life was performed. **RESULTS:** Of the 291 randomized patients, 268 patients completed the trial. The SVR rates were higher in patients treated with PEG-IFN a-2a (74% vs 59%, P = 0.047). More patients treated with PEG-IFN a 2a achieved RVR compared to PEG-IFN a 2b (45% vs 26%; P= 0.01; 95% CI 0.03-0.21 respectively). Partial EVR and slow response was more common in patients treated with PEG-IFN a 2b who needed 48 or 72 weeks of treatment. Earlier normalization of ALT was observed with PEG-IFN a 2b compared to PEG-IFN a 2a (median 28 days vs 36 respectively). The 2 regimens showed similar tolerability although dose modifications for neutropenia and depression were more frequent with PEG-IFN a 2b. Compliance and the quality of life scores were higher with PEG-IFN a 2b. Histologic activity diminished and steatosis and fibrosis stabilized in patients with SVR irrespective of the regimen used. In multiple logistic regression analysis, younger age, RVR, cEVR and >2log decline at week 2, fibrosis scores <4 were significantly predictive of SVR. **CONCLUSION:** In patients with chronic hepatitis C genotype 4, PEG-IFN alpha-2a and 2b and ribavirin were comparable for safety and tolerability. Peg-IFN a2a and ribavirin treatment resulted in the highest rates of SVR. RVR and EVR are useful in determining treatment duration.

Efficacy and Safety RESULTS of albinterferon alfa - 2b in Combination with ribavirin in Treatment Naive Subjects with Chronic Hepatitis C Genotype 2 or 3. Y.Benhamou¹⁶; D.R.Nelson¹⁵; W.Chuang¹⁴; et al. Program Number: 1567

BACKGROUND: A phase 3, randomized, active-controlled, multi-center study evaluated the efficacy and safety of albinterferon alfa-2b (albIFN), a genetic fusion polypeptide of albumin and IFN-2b, in treatment-naïve patients with chronic HCV genotype 2 or 3.

METHODS: 933 patients were randomized 1:1:1 to one of the 3 treatment groups, in combination with ribavirin 800 mg/d: albIFN 900 g q2wk; albIFN 1200 g q2wk (dose reduced to 900 g); PEG-IFN2a 180 g q1wk for 24 weeks. The primary endpoint was sustained virologic response (SVR), defined as HCV RNA < 15 IU/mL at wk 48. Randomization was stratified by baseline HCV RNA levels (or < 800,000 IU/mL) and genotype 2 or 3. **RESULTS:** The study achieved the primary endpoint of non-inferiority of SVR for both albIFN 900 g ($p=0.0086$) and albIFN 1200 g ($p=0.0059$). In the intention-to-treat population, SVR rates were 84.8%, 79.8%, and 80.0% in the PEG-IFN2a, albIFN 900 and albIFN 1200 groups, respectively. Predictors of SVR were HCV RNA < 400,000 IU/mL, age <45, BMI < 30, genotype 2, normal GGT, high ALT, no steatosis, F0-2 fibrosis, and Asian region (for PEG-IFN2a). Subgroup analysis showed that in the Asian region, SVR rate was 95.5%, 79.8% and 81.8% for PEG-IFN2a, albIFN 900 and albIFN 1200 groups, respectively, compared with 80.5%, 79.8% and 79.3% in all other regions. The PPV of initial virologic response at Week 2 (IVR; >2 log viral decline or HCV RNA < LOQ) was 83-90%; the PPV of rapid virologic response at Week 4 (RVR; HCV RNA < LOQ) was 86-91%. In PEG-IFN2a, albIFN 900 and albIFN 1200 groups, the rates of IVR were 81.3%, 86.9%, and 85.8%; the rates of RVR were 84.2%, 79.2%, and 85.2% respectively. Safety analyses showed: 1) Rates of serious and/or severe adverse events (AE) were 17.5%, 17.3% and 16.8%; 2) Treatment discontinuations due to AEs were 3.6%, 4.8% and 5.5%; 3) Severe or serious pulmonary events were rare and blinded central review of chest x-rays during treatment showed comparable rates of interstitial lung findings: 5.0%, 6.3% and 5.2%. **CONCLUSIONS:** Albinterferon alfa-2b 900 g administered q2wk demonstrated comparable efficacy to PEG-IFN2a in chronic HCV genotype 2 or 3 patients. The overall incidence of serious or severe adverse events was similar between these two treatments.

Safety and Antiviral Activity of NS5B Polymerase Inhibitor MK - 3281, in Treatment - Naïve Genotype 1A, 1B AND 3 HCV - Infected Patients. D.M.Brainard¹; M.S.Anderson¹; A.Petry¹; et al. Program Number: 1568

BACKGROUND: MK-3281 is a novel non-nucleoside hepatitis C virus (HCV) NS5B polymerase inhibitor with potent and selective in vitro activity against HCV genotypes (GT) 1a/b and 3 HCV. Safety, tolerability, pharmacokinetics (PK), resistance, and antiviral activity were assessed during multiple dose administration in HCV-infected patients. **METHODS:** This was a double-blind, placebo-controlled, serial panel study in 22 treatment-naïve HCV-infected patients who received 800 mg MK-3281 (17 patients: 4 x GT1b, 6 x GT3, 6 x GT1a, 1 x non-typeable [1-NT]) or placebo (5 patients) q12 hr for 7 days. All patients were followed for two weeks post therapy. Safety and resistance evaluations were performed throughout the study. Plasma samples were collected for MK-3281 PK and HCV viral RNA determination (using the Roche COBAS Taqman assay).

RESULTS: There were no serious adverse experiences (AEs) reported. One patient discontinued due to an AE of myoclonus on study Day 2 of approximately 1.5 h in duration, preliminarily judged possibly-related to MK-3281 and rated of severe intensity. Other AEs were limited in number, transient, and rated mild to moderate in intensity with headache the most frequently reported AE. No clinically relevant laboratory safety signals were observed. However, several patients on therapy showed transient reductions in liver function tests. The PK of MK-3281 in HCV-infected patients were similar to previously reported values observed in healthy subjects. Mean maximum reductions from baseline of HCV viral RNA (SEs) were 1.3 (0.15), 3.8 (0.19), and 1.2 (0.16) log₁₀ IU/mL for GT1a/1-NT, 1b, and 3, respectively. No on-treatment viral rebound was observed in any GT 1b patient, while 1 of 6 GT1a and 1 of 6 GT3 patients showed evidence of on-treatment viral rebound. Upon 2 week follow-up, plasma levels of HCV-RNA had returned to baseline levels in all individuals. Resistance analysis was performed on GT1a and GT1b patients. **CONCLUSIONS:**

MK-3281 as monotherapy for 7 days was well tolerated and demonstrated strong antiviral activity against GT1b HCV with no evidence of viral breakthrough. In vivo activity against GT1a and GT3 was limited. These findings support further clinical investigation of MK-3281 for the treatment of chronic HCV infection.

Virologic and Metabolic Responses in Chronic Hepatitis C (CHC) Patients with Insulin Resistance (IR) Treated with Pioglitazone and Peginterferon Alfa - 2a Plus Ribavirin.

J.M.Vierling¹; F.M.Hamzeh²; E.L.Lentz²; S.Harrison³ Program Number: 1571

BACKGROUND: Patients with CHC and IR are less likely to respond to anti-HCV therapy than the general CHC population. The SENSITIZE study was designed to compare virologic responses in patients with CHC and IR who were randomized to receive peginterferon alfa-2a plus ribavirin (P-2a/R) alone or P-2a/R plus the insulin-sensitizer Pioglitazone (Pio). **METHODS:** This is a multicenter, randomized, open-label study designed to treat 240 CHC patients with HCV genotype 1 and IR. Patients stratified by homeostasis model assessment score (HOMA) of >2 - <4 or 4 were randomized to 2 treatment arms. In both arms, patients received P-2a 180 g/wk plus ribavirin 1000-1600 mg/d for 48 wks. In the Pio arm, patients were treated with Pio alone for 16 wks (30 mg/d x 8 wks then 45 mg/d x 8 wks) before adding 48 wks of treatment with PegIFN-2a/R. Following this, patients in the Pio arm continued Pio 45 mg/d for the 24-wk antiviral-free follow-up period to assess SVR. We report interim virologic and metabolic responses in all patients who received 12 wks of anti-HCV therapy. **RESULTS:** To date, 138 patients have been randomized; 60 in the control arm and 59 in the Pio arm. Disparities between the control and Pio arms at baseline (Wk 0) included more patients in the Pio arm who were black (24% vs 12%), had BMI 30 kg/m² (59% vs 50%), ALT >3ULN (22% vs 15%), had a HOMA score 4 (51% vs 47%), had HCV RNA 800,000 IU/mL (83% vs 77%), and had higher fasting insulin levels (108 pmol/L vs 100 pmol/L). Baseline glycemic measures were similar between arms. The mean log₁₀ changes in HCV RNA from baseline to Wks 4 and 12 of anti-HCV therapy in the control arm were -2.5 IU/mL and -4.1 IU/mL versus -1.9 IU/mL and -3.5 IU/mL in the Pio arm. The proportion of patients achieving undetectable HCV RNA (<28 IU/mL) at Wks 4 (RVR) and 12 (cEVR) was 17% (10/57) and 60% (26/43) in the control, versus 6% (2/35) and 45% (10/22) in the Pio arm, respectively. Median changes in HOMA score, insulin, and glucose concentrations from baseline to Wk 12 of anti-HCV therapy were -0.1, -10.5 pmol/L, and -0.1 mmol/L in the control arm versus -1.1, -37.5 pmol/L, and -0.5 mmol/L in the Pio arm, respectively. Five patients (7%) in the control arm and 4 (6%) in the Pio arm withdrew due to adverse events while 16 (24%) controls and 23 (33%) treated with Pio withdrew for non-safety reasons. **CONCLUSIONS:** Insulin sensitization using Pio treatment prior to and during anti-HCV therapy improved several metabolic variables but may provide no additional benefit in virologic responses in CHC patients with IR treated for 12 wks. This ongoing study will determine whether this trend extends over the long-term.

Baseline platelet count predicts Sustained Viral Response (SVR) in the treatment of chronic hepatitis C with PEG - IFN - 2b and ribavirin: RESULTS from the German PEG - IFN - 2b observational study. S.Mauss¹; E.Zehnter²; M.P.Manns⁸; et al. Program Number: 1577

BACKGROUND and AIMS: The degree of liver fibrosis predicts the likelihood of SVR in treatment-naive HCV patients (pts). Since lower platelet levels correlate with advanced fibrosis, we explored the relation of baseline platelet levels with SVR using data from the German Peg-IFN - 2b/ribavirin observational study. This real-life cohort study assessed safety and efficacy of treatment with Peg-IFN -2b 1.5 g/kg/wk plus weight-based ribavirin (800-1200 mg/day) for 24 wks in G 2/3 pts and for up to 48 wks in G 1 pts according to standard of care. **METHODS:** Between 9/2003 and 8/2007, 285 sites enrolled a total of 4130 pts. Treatment-naive pts with completed case report forms, including those who discontinued for non-response or for any other reasons were considered for outcome analysis. Sustained virologic response (SVR)/relapse (REL) was defined as

undetectable/detectable serum HCV-RNA 24 wks after EOT response. **RESULTS:** Data of 2749 pts were analysed. HCV G 1 (N=1571; 57%) had the highest prevalence followed by G 3 (N=963, 35%) and G 2 (N=215; 8%). Overall SVR was 55.1% showing a wide range from 58.1% in pts with high baseline platelets counts (>200.000/mm³) to only 21.1% in patients with thrombocytopenia <100.000/mm³. A similar correlation between baseline platelet counts and SVR was observed in the subgroups of pts with G 1, G 2 and G 3 infection. Thrombocytopenia was associated with marked increases in non-response rates as well as relapse rates (see Table). **CONCLUSIONS:** In this study, a high baseline platelet count was correlated with a higher SVR rate in patients with genotypes 1-3 receiving Peg-IFN-2b and ribavirin therapy.

Pilot study of lead - in nitazoxanide plus pegylated alpha - 2a interferon and ribavirin in HCV - genotype 1 nonresponders with cirrhosis: interim results.

B.Yoffe^{1,2}; K.Gasitashvili²; V.Khaoustov² Program Number: 1580

BACKGROUND: Nitazoxanide is a member of a new class of small molecules, the thiazolides and is a potent inhibitor of HCV in replicon systems. Previous studies in HCV genotype (GT) 4 patients indicate that nitazoxanide (NTZ) may enhance sustained virologic responses (SVR) in HCV patients. The drug is currently in phase II clinical development for HCV treatment. This pilot study is conducted to assess the antiviral activity of lead-in NTZ administered with peg-interferon and ribavirin in treatment experienced cirrhotic patients with HCV-GT1 who failed previous therapy.

METHODS: The study enrolled cirrhotic patients with chronic HCV-GT1 who failed previous therapies with pegylated interferon and ribavirin. Patients with hepatitis A, B or other forms of liver disease, hepatocellular carcinoma, HIV, pre-existing severe depression or other uncontrolled psychiatric disease, significant renal, cardiac, neurologic or other central nervous system disorders were excluded. Patients received NTZ 500 mg twice daily for 4 weeks followed by NTZ plus pegylated alpa-2a interferon (Peg-IFN) 180 mcg/wk and weight based ribavirin (R) for 48 weeks. Physical examination, hematology and chemistry tests, and serum HCV RNA were performed every 4 weeks during treatment. Treatment was discontinued in subjects without ERV at 4+12 weeks and/or detectable HCV RNA at 4+24 weeks of triple therapy. **RESULTS:** Fourteen subjects (13 nonresponders and 1 relapser) with compensated cirrhosis were enrolled. EVR was achieved in 46.2% (6/13) subjects, with 15.4% (2/13) being undetectable. Dramatic differences in responses were observed between African American (AA) and Caucasian (CA). Only one out of 9 AA demonstrated EVR, whereas all five CA showed EVR. Overall the regimen has been well tolerated without early discontinuation. No serious adverse events were reported throughout the study. Four patient developed adverse events including diarrhea (3), rash (2), cellulitis (3), and laryngitis (1). They were mild to moderate and intermittent in nature. None requiring discontinuation of the treatment. Five patients (without EVR) were discontinued due to lack of response. **CONCLUSION:** An interim analysis of this study indicates that treatment with lead-in NTZ in combination with Peg-IFN and ribavirin has demonstrated promising results in these difficult to treat patients.

Response - Guided Therapy (RGT) for Boceprevir (Boc) Combination Treatment? -

RESULTS from HCV SPRINT – 1. P.Y.Kwo¹; E.Lawitz²; J.McCone³; et al. Program Number: 1582

BACKGROUND: HCV SPRINT-1 investigated a 4-week lead-in of PegIntron (P;1.5 g/kg/QW) plus Ribavirin (R;800-1400 mg/day) prior to the addition of Boc (800 mg TID) for 24 or 44 weeks. Analysis of this data may lead to RGT paradigms. **METHODS:** Viral response was assessed by Roche TaqMan (LLD=15 IU/ml) at multiple time points including treatment weeks 4, 8, 12, 24 and 24 weeks post-treatment (sustained virologic response; SVR). **RESULTS:** Patients were all G1 (1a>1b) with 15% African-Americans, 7% cirrhotics and 90% high viral load. W8 virology was available for all 103 patients in each arm. The majority of patients (64%) became negative by week 8 and SVR rates were similar for the long (94%) and short (82%) treatment arms (p=NS). In contrast,

patients who first became negative between week 8 and 16, benefited from longer therapy (SVR 79% vs 21%; $p=0.004$), but represented only 18% of the population. A third group never achieved undetectable HCV-RNA by W16; this group primarily comprises null responders (11/18 in 48W arm) at week 4. **CONCLUSIONS:** The majority of patients (64%) had undetectable HCV-RNA after 4 weeks of triple therapy following the lead-in and had a high rate of SVR (82%) following a shortened 28-week treatment duration. Only 18% of patients first achieving undetectable HCV-RNA after week 8 and before week 16 of therapy benefited from a longer treatment regimen of 48 weeks. These data suggest that only a minority of treatment-naïve G1 patients will require more than 28 weeks of therapy, and response-guided therapy based on week-8 viral response may be a powerful predictive tool to individualize therapy. The SPRINT-2 trial is designed to prospectively confirm this treatment paradigm.

Combination therapy with nucleoside polymerase R7128 and protease R7227/ITMN - 191 inhibitors in genotype 1 HCV infected patients: interim resistance analysis of INFORM - 1 cohorts A – D.

S.Le Pogam¹; M.Chhabra¹; S.Ali¹; et al. Program Number: 1585

BACKGROUND and AIMS: R7128 is a novel nucleoside polymerase inhibitor that displays a high barrier to the development of drug resistance. No R7128 resistance was observed after 2 (monotherapy) or 4 (combined with SOC) weeks. In contrast, during monotherapy with protease inhibitors such as R7227, drug-resistant variants were observed in a subset of patients, which were suppressed with SOC. Viral kinetics from INFORM1 indicated that R7128/R7227 combination effectively prevented viral rebound. The aim of this study was to monitor and evaluate the effect of this combination on the development of resistance after up to 14 days of treatment. **METHODS:** Baseline NS3/4A and NS5B sequence was determined for all patients in INFORM1. For cohort A, sequence encompassing NS5B and NS3/4A and/or NS3 protease (population and clonal) and phenotypic analysis of NS3 and NS5B were performed at the end of the monotherapy treatment (Day 4) and at the end of combination treatment (Day 7). For cohorts B-D (14 day combination therapy), sequence and phenotypic studies were performed on any patient that experienced viral load rebound (0.5 log₁₀ increase of viral load above nadir). **RESULTS:** 48 of 49 patients receiving the R7128/R7227 combination had a continuous viral load decline on treatment. In cohort A, population and clonal sequence and phenotypic analysis showed no evidence of resistance. In cohorts B-D, 1 patient had a 1.4 log₁₀ IU/mL increase in viral load from nadir. Sequence and phenotypic analysis of the NS3 region showed no evidence of R7227 resistance. Viral load for this patient remains undetectable after 12 weeks of SOC. Baseline population sequence of one patient receiving R7128/R7227 revealed the presence of E168 in NS3; an amino acid associated with R7227 resistance. This patient experienced a continuous viral load decline on R7128/R7227 treatment (viral load of 139 IU/ml at day 14). Complete analysis of NS3/4A, NS3 protease and NS5B regions will be reported. **CONCLUSIONS:** Low dose combination therapy of the nucleoside polymerase inhibitor R7128 (that presents high barrier to resistance) with the protease inhibitor R7227 (that presents potent anti-viral activity and a lower barrier to resistance) achieves rapid and sustained antiviral activity without apparent selection of resistance for up to two weeks of treatment. The ability of this DAA combination to reduce HCV viral load even in the presence of pre-existing R7227 resistant variants indicates that this particular drug combination may have unique attributes relative to other combination strategies where two drugs with lower resistance barrier are combined.

Controlled Release Nitazoxanide in Combination with Peginterferon alfa - 2a plus Ribavirin RESULTS in High Early Virologic Response Rates for Treatment of Chronic Hepatitis C Genotype 4.

E.B.Keeffe^{1,2}; A.Elfert³; S.Abousaif³; J.Rossignol^{1,2} Program Number: 1588

BACKGROUND & AIMS: Clinical trials have shown that the addition of nitazoxanide (NTZ) to peginterferon alfa-2a (PegIFN) ribavirin (RBV) significantly improves sustained virologic response (SVR) rates in treatment-naïve patients with chronic hepatitis C genotype 4. A new controlled release

(CR) 675 mg NTZ tablet demonstrated improved pharmacokinetics in a phase I study when administered to normal volunteers at two dosage levels of 675 mg and 1350 mg twice daily, with acceptable tolerability (APASL: Keeffe EB, et al. Hepat Int. 2009;3:49). The aim of the current study was to evaluate the safety and efficacy of two doses of CR NTZ in combination with PegIFN plus RBV for the treatment of chronic hepatitis C. **METHODS:** In this phase II single-center (U Tanta), double-blind, controlled study, 41 treatment-naïve patients with chronic hepatitis C genotype 4 were randomized to receive placebo (n=8) versus CR NTZ 675 (n=17) or 1350 mg (n=16) twice daily for 4 weeks followed by the same regimen plus the addition of PegIFN 180 g weekly and RBV 1000 to 1200 mg daily for 48 weeks. In the three treatment groups, the mean (SD) ages were 43.11, 36.9, and 32.11 years, respectively, and all subjects were white. There were 5, 11 and 10 men, respectively, in the three groups, and body mass index was 28.4, 27.5, and 26.4, respectively. Baseline serum HCV RNA levels were 5.6 ± 0.7, 5.3 ± 0.6, and 5.6 ± 0.5 log₁₀ IU/mL, respectively. Advanced hepatic fibrosis (Ishak 4, 5 or 6) was present in 4/8, 2/17 and 0/16 patients in the three treatment groups, respectively. Interim results, including rapid virologic response (RVR), early virologic response (EVR) and complete EVR (cEVR) rates after 12 weeks of combination therapy (week 16), are reported. **RESULTS:** A median HCV RNA reduction of -4.74, -5.11 and -5.57 for the placebo, low-dose and high-dose groups, respectively, were observed at week 16. There were dose-related increases in RVR (50%, 59% and 63%), cEVR (63%, 82% and 100%), and EVR (63%, 88% and 100%) in the placebo, low-dose CR NTZ and high-dose CR NTZ groups, respectively. NTZ was well tolerated with all adverse events being mild to moderate; there were no serious adverse events or drug discontinuation. **CONCLUSIONS:** Interim analysis of this ongoing hepatitis C trial shows dose-related increases in RVR, cEVR and EVR rates using CR NTZ added to the standard of care, with acceptable tolerability. CR NTZ has the potential to increase SVR rates in comparison to those achieved using standard NTZ in combination with PegIFN plus RBV.

A Phase 1b Dose - Ranging Study of 4 Weeks of PEG - Interferon (IFN) Lambda (PEG - rIL - 29) in Combination with Ribavirin (RBV) in Patients with Chronic Genotype 1 Hepatitis C Virus (HCV) Infection. A.Muir¹; M.L.Shiffman²; A.Zaman³; et al. Program Number: 1591

BACKGROUND: PEG-IFN-lambda (PEG-rIL-29) is a unique interferon that has fewer flu-like symptoms and hematologic adverse effects than are typically observed with alpha IFNs, likely due to more focused expression of the IFN-lambda receptor. A Phase 1b study of PEG-rIL-29 in HCV genotype 1 patients who relapsed after treatment with IFN-alpha + RBV or are treatment-naïve is ongoing. Initial results previously presented demonstrated that weekly administration of PEG-rIL-29 as a single agent was well-tolerated and associated with greater HCV RNA reduction than every other week administration. **METHODS:** This open-label dose-ranging study is evaluating 4 weeks of PEG-rIL-29 administered QW subcutaneously in combination with daily RBV (1000 or 1200 mg/day) in patients with HCV genotype 1 and prior relapse. A treatment-naïve cohort is currently being enrolled. Assessments include adverse events (AEs), laboratory values, and changes in HCV RNA. **RESULTS:** A total of 16 patients with chronic HCV and prior relapse have completed 4 weeks of treatment with PEG-rIL-29 QW (0.5 [n=4], 0.75 [n=3], 1.5 [n=6], and 2.25 [n=3] g/kg) and daily RBV. Treatment has been well-tolerated with minimal flu-like symptoms and no significant hematologic changes other than RBV-associated decreases in hemoglobin. The most common AEs, regardless of dose level, are fatigue (4/16; 25%), nausea (4/16; 25%), and insomnia (3/16; 19%), all Grade 1 or 2. As previously reported, one patient treated at PEG-rIL-29 1.5 g/kg QW + RBV experienced reversible Grade 3/4 increases in ALT, AST, and bilirubin. No other patient receiving PEG-rIL-29 + RBV has experienced clinically-significant elevations in these parameters. Dose-dependent antiviral activity in patients completing 4 weeks of treatment has been observed at all dose levels, with 12/16 (75%) relapse patients achieving > 2-log decrease (range 0.1-5.6) in HCV RNA, and all 3 subjects treated at 2.25 g/kg achieving HCV RNA levels < 1000 IU/mL at Day 29.

CONCLUSIONS: PEG-rIL-29 QW subcutaneously + daily RBV administered for 4 weeks has been well-tolerated with minimal flu-like symptoms or hematologic effects in patients with chronic HCV and prior relapse. This treatment is also associated with robust antiviral activity across a broad range of doses.

Clonal analysis of mutations selected in the HCV NS3 protease domain of genotype 1 non-responders sequentially treated with boceprevir (SCH503034) and/or pegylated interferon alfa - 2b (PEG - IFN - 2b). J.Vermehren¹; S.Susser¹; U.Karey¹; et al. Program Number: 1592

BACKGROUND: Boceprevir (BOC) is a highly selective inhibitor of the hepatitis C virus (HCV) NS3/4A protease. Mutations have been identified in the NS3 protease gene at positions 36, 54, 55, 155, 156 and 170 conferring resistance to BOC in vitro and in vivo. The resistance profile of BOC/PEG-IFN -2b combination therapy as well as the kinetics of resistant variants during sequential treatments are unknown. **METHODS:** Twenty-six nonresponders to PEG-IFN -2b ribavirin treatment were randomized to different sequences of three periods of treatment with BOC monotherapy (200mg or 400mg TID) for 7 days, PEG-IFN -2b monotherapy once weekly for 14 days and combination of the two for 14 days. Between the different treatment schedules therapy was interrupted for 14 days (Sarrazin et al., Gastroenterology 2007). In the present study, we performed amplification and clonal sequencing of the NS3 protease gene in 4 patients at baseline and at the end of each treatment period showing BOC resistant mutations during sequential treatment with BOC alone or in combination with PEG-IFN -2b. **RESULTS:** If patients were initially treated with BOC monotherapy, resistant variants at one or more of six known amino acid positions of the NS3 protease (36, 54, 55, 155, 156, 170) were observed. At baseline and during the following combination therapy of BOC and PEG-IFN -2b resistance mutations were still detectable in some patients. During an initial combination therapy with BOC and PEG-IFN -2b known resistant variants were also selected. These mutations, including the highly resistant A156T variant, were also detectable during subsequent monotherapy with boceprevir. Between the different treatment schedules the frequency of resistant variants declined rapidly but mutations conferring resistance at low levels were still detectable before initiation of the next treatment schedule in some patients.

CONCLUSIONS: Resistant variants to BOC are selected during monotherapy and combination therapy with PEG-IFN -2b. During combination therapy with BOC and PEG-IFN -2b a continuous viral decline was observed irrespective of the selection of resistant variants. In patients with resistant variants detectable after BOC monotherapy at low frequencies a rapid selection of these variants was observed during re-treatment with BOC in combination with PEG -2b in some patients.

Pharmacokinetics/Pharmacodynamics (PK/PD) of Combination R7227 and R7128 Therapy From INFORM - 1 Demonstrates Similar Early HCV Viral Dynamics When R7227 is Combined With Either PEG - IFN/Ribavirin (SOC) or R7128. P.N.Morcos¹; R.Kulkarni¹; D.Ipe¹; et al. Program Number: 1594

INTRODUCTION: INFORM-1 is evaluating a nucleoside polymerase inhibitor (R7128) & protease inhibitor (R7227) combination, offering the potential for a highly potent regimen & high resistance barrier. Our objective was to evaluate the PK/PD of R7227 when combined with either R7128 or SOC. **METHODS:** 61 HCV-infected (G1) treatment nave patients (pts) received up to 14d oral combination R7128/R7227 with escalating doses of either 500 or 1000 mg bid R7128 & 100, 200mg tid or 600mg bid R7227 or placebo (N=8 active, 2 placebo). Frequent sampling for PK & HCVRNA was done in all pts. PK/PD & viral kinetics were compared to a simil study of R7227 + SOC in treatment nave pts (Zeuzem EASL 2009) **RESULTS:** The combination of R7128/R7227 demonstrated potent antiviral activity with ~5 Log₁₀ HCVRNA reduction from baseline at D14 in higher dose cohorts. The PK of R7227 & R7128 was not altered when combined. An Emax PK/PD model of R7227 C_{min} vs D14 Log₁₀ HCVRNA change from baseline fit the

data well for R7227 with either R7128 ($r^2 = 0.92$) or SOC ($r^2 = 0.85$). EC50 and Emax values were similar for R7227 added to either R7128 or SOC. For R7227/R7128, pts with R7227 Cmin > 0.5 ng/mL had similar antiviral responses with either 500 or 1000mg R7128 (d14 median HCVRNA change = -5.1 Log10 IU/mL). For R7227 Cmin < 0.5, patients receiving 500mg R7128 had a median HCVRNA change of -3.5 Log10 IU/mL compared to -4.8 with 1000mg. Median -half-life & -phase slopes for R7227 added to either R7128 or SOC are shown in the table, demonstrating similar profiles. **CONCLUSION:** The addition of R7128 to R7227 provided similar PK/PD & early viral kinetic profiles compared to the addition of SOC to R7227. R7128 demonstrated a dose-dependent enhancement of R7227 activity, particularly at lower R7227 exposures. The similarities in beta phase slopes during the 2nd phase of viral clearance when R7227 is used with SOC or R7128 indicates that viral suppression is similarly sustained over 14d for both combination regimens. This analysis supports the observation that in both types of regimens the emergence of R7227 resistance is suppressed. These results support the continued development of this novel direct-acting antiviral combination

Aging of Hepatitis C Infected Persons in the United States: A Multiple Cohort Model of HCV Prevalence and Disease Progression. G.L.Davis¹; M.J.Alter²; H.B.El-Serag³; T.Poynard⁴; L.W.Jennings¹ Program Number: 1613

BACKGROUND: New infections with the hepatitis C have decreased markedly in recent years, but the prevalence of chronic infection (CH-C) remains high and the consequences of the disease are becoming more common. Some studies suggest that the burden resulting from complications of CH-C has reached a plateau while others predict a rise in cirrhosis and its complications for another 2 or 3 decades. **METHODS:** Previous models of CH-C were limited by the need to consider infected patients as a homogeneous group who progressed in a fixed and typically linear fashion over time. To address these limitations, we developed a multilayered parallel modeling approach comprised of 6 age-gender cohorts that also allowed input of new cases by year and changes in progression rates by age, gender, and/or duration of infection or cirrhosis. Cohorts included ages <30 yrs, 31-50 and >50 yr for each gender. **RESULTS:** Cohort analyses confirmed previous observations of cirrhosis rates in young females and males, as well as older males. Estimated prevalence in 1994 was consistent the NHANES-base estimates. The model showed that the prevalence of CH-C peaked in 2001 at 3.6 million and is projected to reach about half this number by 2030. We estimate there are currently approximately equal numbers of infected patients have minimal-to-mild (F0 or F1) and advanced (F3 or F4) fibrosis. Fibrosis progression was inversely related to age at infection, so cirrhosis and its complications were most common between the ages of 60 and 80, regardless of when infection occurred. The proportion of surviving infected persons who have cirrhosis is projected to reach 25% in 2010 and 45% in 2030, though the total number with cirrhosis should peak at 1.0 million (30.5% higher than the current level) in 2020. The number with decompensation will continue to increase until 2022. Using conservative cancer risk estimates, hepatitis C-related liver cancer will peak in 2019 at 14,000 cases per year if the risk in persons with fibrosis remains stable. **CONCLUSION:** We estimate the current prevalence of chronic hepatitis to be 3.5 million persons. The number with cirrhosis and its complications will continue to increase for at least another decade and will impact mostly those over the age of 60 years. The face of CH-C in the 1990s will be very different from its face in over the next two decades. This may have significant implications for our healthcare system and emphasizes an urgent need for screening and early antiviral treatment.

Early loss of exposure to Estrogens is critical in determining entity of fibrosis and response to IFN in women with hepatitis C. A.Karampatou¹; P.Pazienza¹; B.Lei¹; et al. Program Number: 1615

Post-menopausal (post-M) women were reported to have accelerated progression fibrosis. As menopause coincides with aging and longer duration of infection, it is not clear which is the key factor in determining worsening of disease. We analyzed a consecutive series of 945 patients with hepatitis C undergoing PEG IFN alpha+Ribavirin (RBV) in relation with EVR and SVR focusing on the influence of age, menopause, type of menopause (spontaneous, surgical) and associated metabolic characteristics. Patients-**METHODS**: 945 patients [541 M, 404 F (252 menopausal, 50 surgical, 202 spontaneous)] with biopsy-proven CAH, consecutively treated with PEG IFN alpha 2b 1,5 ug/kg/wk or 2a 180 ug plus RBV 800-1200 mg/day were evaluated. Undetectable HCV RNA at end of treatment (48 wks for gt 1, 3 or 4 or previously non responders and 24 wks for nave gt 2) defined EVR and 6 months of f-up defined SVR. **RESULTS**. Genotype distribution was even. Weight was lower in pre-menopausal (pre-M) women vs. post-M (median 61 vs.64 kg); however histological steatosis was not significantly different between pre- and post-M women. Both EVR and SVR were significantly higher in pre-M women vs males (EVR: 70% vs 57%, p=.006; SVR 63% vs 51%, p=.007) and vs post-M women (EVR: 70% vs. 53%, p=.004; VR 63% vs. 47%, p=.038). No significant difference in EVR and SVR was found between males and post-M females. Median age of pre-M females was 41 years. Median age of surgical post-M women was significantly lower than of spontaneous menopause (p=.028); median age at menopause was 42 (surgical) vs. 51 years (spontaneous). Although length of infection was significantly shorter in surgical vs. spontaneous menopausal women (p=.000) fibrosis was as severe in surgical than in spontaneous post-M women (1.930.16 vs. 2.130.16; p=NS). For both surgical and spontaneous post-M women vs pre-M women, fibrosis was more severe (mean Ishak stage: surgical vs. pre-menopause 1.930.16 vs. 1.40.1 (p=.000) or spontaneous 2.130.16 vs. 1.40.1 ; p=.004). Fibrosis in pre-M women of comparable age to post-M women was significantly lower than in these (1,61.1 vs. 2.61.0; p=.003). No significant difference was evidenced in grading. **CONCLUSIONS**. Menopause and early menopause play a significant role in determining the severity of fibrosis, independently from age of the women studied. These data underline the critical role played by Estrogens as modulators of inflammation and immunity and the relevance of their early loss. The striking difference in response to IFN strongly indicates that IFN therapy should be started at the youngest possible age and in any case before menopause.

Incidence of end - stage liver disease and death among 585 HIV/HCV coinfecting adults according to baseline fibrosis stage. M.S.Sulkowski1; B.Limketkai1; S.H.Mehta2; et al. Program Number: 1617

BACKGROUND. Although liver biopsy is recommended for staging HIV/HCV infected persons, the degree to which histologic stage predicts clinical outcomes is unknown. The study objective was to assess the incidence of clinical liver disease and death according to hepatic fibrosis stage in HIV/HCV adults. **METHODS**. HIV/HCV adults in the Johns Hopkins HIV clinic have been observed following liver biopsy for histologic (cirrhosis) and clinical outcomes (ESLD, mortality). Liver biopsies were assessed by a single pathologist and scored using the METAVIR system. Laboratory data were collected electronically; clinical outcomes were abstracted from medical records. The primary endpoints were: progression to cirrhosis, ESLD, or death from time of the baseline liver biopsy. **RESULTS**. 585 adults were followed for a mean of 75.6 months (range 12-156). At baseline, the median age was 45 yrs; 65.6% were male; 80.3% were Black; 17% had METAVIR stage 3/4 fibrosis (Table). Patients with advanced fibrosis (stage 3-4, 19.1% of 99) were ten-fold more likely to progress to ESLD than persons with more minimal liver fibrosis (stage 0-1) (5 of 486, 1.2%; RR 10.2, 95% CI 4.6 - 22.8, P < .0001). Deaths occurred more often in those with stage 3-4 fibrosis at baseline compared to those with less fibrosis (stage 0-1)(35.1% > 14%, RR 2.2, 95% CI 1.58 - 3.14; P < .0001). Incident cirrhosis was observed in 8.8% of patients with no or stage 1 fibrosis and 30.5% of those with stage 2 fibrosis. **CONCLUSIONS**. While these findings demonstrate the prognostic value of liver histology in HIV/HCV persons, they also underscore the high risk of clinical outcomes, even among those with relatively mild baseline disease.

Natural clearance of hepatitis C virus (HCV) RNA in chronic HCV carriers: A long - term cohort study in an endemic area of HCV infection in Japan. H.Watanabe¹; T.Saito¹; Y.Nishise¹; et al. Program Number: 1619

BACKGROUND: The outcome of hepatitis C virus (HCV) infection varies among individuals and has not been fully elucidated. It remains unclear whether HCV viremia can be spontaneously eliminated from persistently infected individuals in the natural course of HCV infection. Recently, highly-sensitive HCV RNA detection system using a real-time PCR method has been developed and applied for the clinical use. We investigated the incidence of spontaneous disappearance of serum HCV RNA by the real-time PCR and analyzed the risk factors associated with the HCV clearance.

METHODS: To investigate the incidence of spontaneous elimination of serum HCV RNA, a long-term cohort study in an endemic area was conducted on 475 chronic HCV carriers (mean age; 66.69.4 years old) without a history of antiviral therapy or without seropositivity for hepatitis B surface (HBs) antigen. Subjects were followed up for 16.00.16 years (95% confidence interval (CI) 15.7-16.4) since 1991. Individual characteristics (gender and age), liver function tests (AST, ALT, -GTP and ZTT), anti-HBs seropositivity, anti-HCV titer, HCV genotypes, and serum HCV RNA detected by using the TaqMan HCV real-time PCR assay (Nippon Roche, Tokyo, Japan) were analyzed using blood samples. The persistence of resolution was confirmed over a minimum of 12 months by independent sampling. Cumulative incidence curve was estimated by use of the Kaplan-Meier method, the risk of spontaneous HCV elimination was evaluated by use of the Cox proportional hazard model. The present study was approved by the Ethical Review Committee of Yamagata University, and written informed consent was obtained from all the subjects recruited.

RESULTS: Serum HCV RNA was spontaneously eliminated in 34/475 (7.2%) individuals during this period. The 5-year cumulative incidence of spontaneous elimination of serum HCV RNA was 0.047 (95%CI, 0.031-0.072), the 10-year rate was 0.071 (95%CI, 0.049-0.103), and the 15-year rate was 0.111 (95%CI, 0.075-0.163) in a population. Multivariate analysis revealed that both a low value of ZTT (hazard ratio (HR), 9.95; 95%CI, 2.99-33.98) and a low titer of anti-HCV antibody (HR, 1.08; 95%CI, 1.05-1.10) were significantly associated with spontaneous HCV elimination ($p < 0.001$). **CONCLUSION:** These results suggest that serum HCV RNA is naturally cleared in a population, with an estimate of its incidence, from a long-term cohort study of chronic HCV carriers. Spontaneous elimination occurs in individuals without evidence of liver disease, or in those with a low titer of anti-HCV antibody. These findings contribute to a better understanding of the natural history of HCV infection in population.

Insulin Resistance and Hepatic Steatosis are Both Independently Associated with Advanced Hepatic Fibrosis in Chronic Hepatitis C Infection: Analysis of the ACHIEVE 1 and

ACHIEVE 2/3 Cohorts. A.J.Thompson²; K.Patel²; H.L.Tillmann²; et al. Program Number: 1622

BACKGROUND: Hepatic fibrogenesis is a complex, multifactorial process. The relative roles of insulin resistance (IR) and hepatic steatosis in fibrogenesis in chronic hepatitis C infection (CHC) has been a recent topic of debate, and conflicting data have been published. We therefore investigated the relationship between IR, hepatic steatosis and hepatic fibrosis in patients enrolled in the ACHIEVE 1 and ACHIEVE 2/3 trials. **METHODS:** 2255 treatment-naïve patients with chronic HCV-1 or HCV-2/3 were enrolled in two separate phase 3, active-controlled studies of albinterferon alfa-2b plus ribavirin for 48 or 24 weeks, respectively. IR was measured at baseline using the homeostasis model for assessment (HOMA-IR). Baseline liver biopsy was evaluated for steatosis, METAVIR grade and fibrosis stage by a single expert histopathologist. Advanced fibrosis was defined as METAVIR stage F2-4. Steatosis was scored as grade 0 (5% steatosis), 1 (6-30%), 2 (31-60%) and 3 (>61%). Other clinical variables considered included age, gender, race, body mass index (BMI), alcohol history, HCV viral load, HCV genotype and serum total cholesterol level. Independent factors associated with advanced hepatic fibrosis were modeled using logistic

regression with backwards elimination (SAS v9.1 statistical software). **RESULTS:** A complete data set was available for analysis in 1515 non-diabetic patients (HCV-1 = 819, HCV-2 = 327, HCV-3 = 369). The prevalence of METAVIR stages in our cohort were F0=546 (37%), F1=680 (46%), F2=117 (8%), F3=74 (5%) and F4=76 (5%). The prevalence of steatosis was grade 0=1058 (70%), grade 1=329 (22%), grade 2=81 (5%) and grade 3 = 34 (2%). Median HOMA-IR was 2.0 (IQR 1.3 - 3.6). The factors identified by multivariable logistic regression to be independently associated with advanced fibrosis were: age, HOMA-IR, hepatic steatosis grade, hepatic inflammatory grade and serum total cholesterol levels (TABLE 1). **CONCLUSION:** In this large, well characterized cohort of CHC patients, advanced hepatic fibrosis was independently and positively associated with both insulin resistance and hepatic steatosis, in addition to age and hepatic inflammation. Serum total cholesterol was independently but negatively associated with advanced fibrosis.

Hepatitis C and menopause: interplay of age, gender, HCV replication and activity in progression and consequence for therapy. E.Trpo1; F.Bailly2; C.Moreno1; et al. Program

Number: 1631

BACKGROUND and AIMS: Main factors associated with fibrosis progression in patients with chronic hepatitis C (CHC) infection include age, gender, duration of disease, initial fibrosis stage, steatosis and alcohol consumption. Previous studies indicate that menopause also impacts on pace of progression and that estrogens could have an antifibrogenic effect. The objective of this study was to assess precisely how the effect of gender varied according to age and to better clarify menopause-associated changes. **METHODS:** CHC patients enrolled at the Hpital Erasme, Brussels, Belgium, and Hotel-Dieu, Lyon, France, were retrospectively analyzed. Patients were classified as progressors if they showed a METAVIR fibrosis score of at least F3 and as non-progressors if they remained below F3 at sequential histological assessments after at least 5 years of follow-up. Patients with confounding progression factors such as heavy alcohol consumption were excluded.

RESULTS: 163 patients were studied. Mean age was 55 years (range 23-84), 56% were males, and 55% were classified as progressors. Male gender was associated with fibrosis progression (66% of males were progressors versus 41% of females, $p=0.001$). Below 50 years ($n=67$), 51% of males were progressors compared with 11% of females ($p=0.001$) whereas over 50 years ($n=96$), 77% of males were progressors versus 61% of females ($p=0.08$). Similar statistically significant differences were observed for activity (35% of women below 50 years of age had a METAVIR activity score ≥ 2 versus 64% in women above 50; $p=0.015$). Irrespective of gender, viral load was significantly lower in patients over 60 years of age than in patients below 60 (4.1 log₁₀IU vs 5.2 log₁₀IU; $p=0.03$). In women below 60, viral load was rather constant before 50 years but substantially increased over 50 ($p=0.06$). In multivariate analysis, age >50 (OR=4.2; $p<0.001$), male gender (OR=3.5; $p=0.001$), and activity ≥ 2 (OR=2.9; $p=0.004$) were significantly associated with fibrosis progression whereas viral load had no impact on progression. **CONCLUSIONS:** The association between fibrosis progression and gender is strong in patients below 50 years of age but decreases after. This study suggests a possible benefit of estrogens in younger women with CHC, probably through an antifibrogenic/antiinflammatory action. The mechanism of HCV RNA increase in women over 50 years remains to be explained. Contrary to precautionary unsubstantiated practice, these observations should favor the use of estrogen replacement for earlier therapy in menopausal women.

Decrease in platelets, while still within normal range, correlate with increase in hepatic fibrosis in chronic hepatitis C infection. A.A.Pereira; B.Aden; M.Gambarin-Gelwan; et al.

Program Number: 1638

STUDY PURPOSE: It is well established that portal hypertension is associated with thrombocytopenia, but whether decreases in platelet counts while still in the normal range (150-350 K/mcL) are associated with advanced fibrosis has not been determined. We performed this study to

evaluate the association between normal platelet counts and hepatic fibrosis on serial liver biopsies in patients with chronic hepatitis C (CHC) infection. **METHODS** We retrospectively reviewed case records of patients with CHC, platelet counts within normal range and paired liver biopsies from 2000-2008. Exclusion criteria were blood dyscrasias, successful treatment of CHC, liver transplant recipients and co-existent liver disease (except HIV). Liver biopsies were reviewed by staff pathologists at our institution. Platelet counts were obtained within 3 months of the liver biopsy. Statistical analyses were performed using SAS (version 9.1). **RESULTS** A total of 160 patient records were reviewed and 31 patients with subsequent platelet counts < 150,000 and were excluded. Of the remaining 129 patients, 80 were HCV mono-infected and 49 were HCV/HIV co-infected. Co-infected patients were mostly male (73% vs 52%), younger age (49 years vs 53 years) and had a higher baseline fibrosis stage (2 vs 1) compared to mono-infected individuals. The two cohorts did not differ significantly with regards to baseline platelet count. Receiver operator characteristic curve analysis revealed a cut-off of >25,000 (decrease in platelet count) to be associated with the most favorable sensitivity (0.44), specificity (0.80), positive predictive value (0.72) and negative predictive value (0.56) for progression of fibrosis. Multivariate logistic regression analysis using this cut-off and controlling for age, gender, baseline platelet count, baseline stage, time between biopsies and HCV mono-infection vs HCV/HIV co-infection, was performed. With a > 25,000 decrease in platelet count, the OR for progression of fibrosis in the overall cohort was 3.4 (CI 1.32, 8.77), 1.93 (0.61, 6.11) in the HCV mono-infected and 29.14 (2.60, 326.54) in the co-infected. **CONCLUSIONS** Within the normal range, decreases in platelet count of >25,000 are associated with an increase risk of progression of hepatic fibrosis in CHC and is most pronounced in the HCV/HIV infected population. Thus, a decrease in platelet count while still within normal limits may provide valuable clues to guide frequency of subsequent histological assessment liver biopsies in CHC.

Self - reported cognitive symptoms are commonly associated with underlying neurocognitive impairment in hepatitis C infected patients referred for antiviral treatment.

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BACKGROUND: Depression, fatigue and difficulties with memory, attention and concentration ("brain fog") are commonly reported in chronic hepatitis C virus (HCV) infection. Cognitive impairments have been demonstrated in HCV-infected patients but no link between self-reported symptoms and objectively measured performance has been shown, possibly because commonly used assessments (eg SF36) are insensitive to cognitive symptoms. Purpose: To evaluate neuropsychological symptoms in treatment naive HCV patients with mild liver disease and to determine whether these relate to performance on cognitive testing. **METHODS:** 34 HCV RNA+ve, HIV-ve, non-cirrhotic patients were recruited from a specialist hepatitis clinic. Subjects completed a computerised cognitive testing battery (Cognitive Drug Research, UK) after appropriate training and were compared to age and sex matched normative data. Cognitive symptoms were evaluated with the Cognitive Function scale from the Medical Outcomes Survey (MSCOG), depression with the Beck Depression Inventory (BDI) and fatigue with the Fatigue Impact Scale (FIS). Routine blood samples were collected. **RESULTS:** The mean (SD) age of the cohort was 45 (9.6) years, males 68%, females 32%. 17 patients had a liver biopsy (Ishak: F0 (2), F1 (5), F2 (3), F3 (3), F4 (4)); all others had clinically mild liver disease. 50% had a history of illicit drug use (median time since last use: 20yrs). No subject was taking CNS altering medication. There were significant impairments (>2 SD below normative mean) in the speed of memory score (n=16 (47%) and power of attention n=5 (15%)). Impaired patients had significantly worse MSCOG than non-impaired (68.7 (18.0) v 87.8 (16.1), p=0.002). 10/11 patients (91%) with a MSCOG<75 had significant cognitive impairment (positive predictive value). This cut off had a sensitivity of 63%, specificity of 94%, negative predictive value of 74% and AUROC of 0.81, p=0.002. There were no significant associations between MSCOG<75 and age, ethnicity, years of education (< or > than 12) or

duration of infection. Subjects with a history of drug use were less likely to have MSCOG<75 ($p=0.023$). MSCOG<75 was significantly associated with mild depression (BDI>11, $p=0.007$) and fatigue (FIS>35 $p=0.02$). **CONCLUSIONS:** We demonstrate a strong association between perceived and actual cognitive impairment in HCV infection, unrelated to a number of confounders. The association with depression and fatigue warrants further study. We propose a MSCOG score <75 as an accurate tool to detect cognitive impairment and suggest that this helpful score should be incorporated into the quality of life assessment in prospective treatment studies.

Predictive factors of hepatocellular carcinoma in patients with HCV - related advanced fibrosis and sustained virological response. A.F.Cardoso; R.J.Carvalho-Filho; C.Stern; et al.
Program Number: 1726

Recent studies have shown that sustained virological response (SVR) to HCV antiviral therapy reduces liver-related complications, particularly in those with advanced liver fibrosis. However, hepatocellular carcinoma (HCC) has been described in these patients, despite the absence of HCV replication. **The aim** of this study was to identify predictive factors associated with the development of HCC in HCV subjects with SVR. **METHODS:** This was a retrospective analysis of consecutively treated patients with chronic hepatitis C who had biopsy-proven advanced fibrosis or cirrhosis (F3 or F4, METAVIR scoring system). All patients achieved SVR under interferon plus ribavirin combination therapy (HCV RNA negative by TMA 24 weeks after treatment discontinuation). HCC screening was performed by alpha-fetoprotein and ultrasound scan at 6-month intervals. Twelve cases of HCC were diagnosed based on histological confirmation and/or typical imaging findings. 114 patients with F3/F4, treated during the same period, and who developed SVR without HCC served as controls. **RESULTS:** The characteristics of the overall population of 126 patients were: mean age 48.411.3 yrs, 71% males, 68% of Caucasians, and obesity in 16%. Genotypes 1/4/5 were observed in 53% and 71% subjects showed F3 stage. The median follow-up was 6.0 yrs (IQR, 4.4 - 8.1 yrs). All patients with HCC were males and all exhibited biochemical response after treatment. Fifty-three percent of these patients were F3. HCC was diagnosed between 0.5 and 6.8 yrs post treatment (median, 2.3 yrs; IQR, 1.4 - 4.9 yrs). Single nodules were seen in all cases, 7/12 (58%) had diameter 3.0 cm, and 71% were well-differentiated. By univariate analysis, HCC was associated with age 50 yrs ($P=0.015$), male gender ($P=0.018$), gastroesophageal varices ($P=0.016$), lower levels of prothrombin activity ($P=0.004$), and with higher levels of alpha-fetoprotein ($P=0.007$). By logistic regression analysis, age 50 yrs (OR, 8.50; CI95% 1.09 - 66.0) and low prothrombin activity (OR, 0.92; CI95% 0.86 - 0.98) were independently associated with the development of HCC. **CONCLUSIONS:** The observation of HCC as late as 6.8 yrs after therapy justifies the recommendation of close follow-up of HCV patients with advanced liver fibrosis or cirrhosis who achieve SVR. Age 50 yrs and lower prothrombin activity are significant predictors of HCC development.

Latent hepatitis B is an additional risk factor for hepatocellular carcinoma in cirrhotic patients with chronic hepatitis C. A.Reddy; M.G.Mutchnick; M.N.Ehrinpreis; E.J.May; F.A.Siddiqui Program Number: 1770

BACKGROUND: Patients with chronic hepatitis C (CHC) and cirrhosis have an increased risk of developing hepatocellular carcinoma (HCC). Risk factors for HCC in these patients are only partially understood. We studied the potential association between HCC and latent hepatitis B (LHB) infection, defined as the absence of detectable serum HBsAg and the presence of HBcAb, in patients with CHC and cirrhosis. **METHODS:** This is a retrospective study of 108 HCV RNA-confirmed CHC patients with HCC, who were HBsAg(-), at Harper University Hospital between 1999 and 2008. Controls were drawn from a database of hepatitis C patients seen at our institution and consisted of 356 HBsAg(-), age, race and gender matched patients with HCV RNA-confirmed CHC, without evidence of HCC, from the same time period. One hundred one CHC controls had

cirrhosis. 2 test and paired T test were used for data analysis. **RESULTS:** When compared to CHC controls, patients with HCC had a significantly higher BMI ($p=0.03$), a higher rate of co-infection with HIV ($p=0.05$) and a higher prevalence of alcohol abuse ($p=0.03$). More patients with HCC had LHB than in CHC controls (75% vs. 39.3%; $p=0.01$, See Table). Sixty-seven percent of patients with HCC were both HBsAb(-) and HBcAb(+) compared to 21 % in CHC controls ($p<0.01$). When compared to cirrhotic CHC controls, the frequency of HBcAb(+) remained higher in patients with HCC (75% vs. 48.6%; $p=0.02$). More patients with HCC were both HBsAb(-)and HBcAb(+) than in cirrhotic CHC controls (66.7% vs. 32.6%; $p<0.01$). Although not statistically significant, all CHC and HIV co-infected patients with HCC ($n = 11$) were HBcAb(+) when compared to controls (44.4%; $n = 9$). **CONCLUSIONS:** These data suggest that LHB infection is not only associated with cirrhosis but also an additional risk factor for HCC in patients with CHC. Furthermore, patients with CHC and LHB who are HBsAb(-) may have an even greater propensity for the development of hepatocellular carcinoma.