

HEPATITIS C CARING AMBASSADORS PROGRAM NEWSLETTER
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IN THE NEWS

Valeant Pharmaceuticals Agrees to Acquire Rights to Hep-C Drug Infergen® from InterMune

http://www.genengnews.com/news/bnitem.aspx?name=1114732XSL_NEWSML_TO_NEWSML_WEB.xml

Valeant Pharmaceuticals International today announced that it has signed a definitive agreement to acquire the United States and Canadian rights to the hepatitis C drug Infergen® (interferon alfacon-1) from InterMune, Inc. Valeant will pay InterMune \$113.5 million in cash upon closing, and subsequent milestone payments of up to approximately \$22.5 million. Valeant also will acquire an estimated \$6.5 million in inventory from InterMune. The transaction was approved by Valeant's board of directors and is expected to close following the expiration or early termination of the waiting period under the Hart-Scott-Rodino Antitrust Improvement Act of 1976, as amended. Closing is expected in late 2005.

"The acquisition of Infergen will have an immediate sales impact on Valeant and provide us with a valuable addition to one of our core therapeutic areas," said Timothy C. Tyson, Valeant's president and chief executive officer. "In addition, we intend to hire up to 50 of InterMune's sales and marketing force, which will help to provide Valeant with an immediate presence in the hepatitis C market and position us for the anticipated launch of Viramidine®." Viramidine, which is currently in Phase 3 clinical trials, is expected to be launched in 2007.

Infergen or consensus interferon, is a bio-optimized, selective and highly potent type 1 interferon alpha originally developed by Amgen and launched in the United States in 1997. It is currently indicated as monotherapy for the treatment of adult patients suffering from chronic hepatitis C viral infections with compensated liver disease and is dosed three times per week. Infergen is the only interferon with data in the label regarding use in patients following relapse or non-response to certain previous treatments. Infergen is being studied in ongoing clinical trials to establish additional labeling for daily use with ribavirin. Enrollment in the Phase 3 IHRC-001 (DIRECT) trial was completed in mid-2005 with 514 patients at 40 sites in the United States. The DIRECT trial, which should be completed in 2007, is evaluating the safety and efficacy of both 9mcg and 15mcg doses of daily Infergen in combination with ribavirin in non-responders. Management of the DIRECT trial will be transitioned from InterMune to Valeant following the closing of the transaction.

Sales of Infergen were \$22 million in 2004. For the first nine months of 2005, sales of Infergen increased by 79 percent to \$25.3 million compared to \$14.2 million for the first nine months of 2004. The acquisition of Infergen is expected to be neutral in 2005, excluding the impact of acquired in-process research and development, which is estimated to be approximately \$45 million, and modestly dilutive in 2006.

Firefighters Volunteer for Hepatitis C Testing

<http://www.shreveporttimes.com/apps/pbcs.dll/article?AID=/20051201/NEWS01/512010331/1002/NEWS>

"By the nature of their job, they are at risk," said Katherine Auble, executive director of the American Liver Foundation, who is in Shreveport administering the test. Hepatitis C, a blood-borne virus, is transmitted by direct exposure to contaminated blood. Firefighters and EMS personnel are more likely to come in contact with blood than other professions, Auble said.

Across the nation there have been reports of large numbers of city firefighters having tested positive for the disease, including Philadelphia -- where firefighters have tested positive at a rate three times the national average. And because of that, local firefighters think the testing is a good idea.

"We want to be proactive in our efforts to protect our members from infectious diseases like hepatitis C and HIV," Fire Chief Kelvin Cochran said. "Recent evidence has caused us to be concerned that our members may have been unknowingly exposed to hepatitis C through contact with contaminated blood during rescues and on medical calls." While firefighters do their best to avoid direct contact with other people's bodily fluids, that wasn't always the case. Before 1992, the use of gloves and face and eye guards were not so common. But firefighter Todd Olague, who was tested Wednesday at the Shreveport Regional Fire Training Academy, isn't nervous. "I feel like we have always protected ourselves the best we can as a department in general," the 10-year veteran said.

More than 250 firefighters have been screened this week and another 250 are expected to have passed through by Friday. Roche, a Switzerland-based pharmaceutical company which produces a drug used to treat hepatitis C, is paying the \$8,000 bill to test for the virus. But the test is not about finding new customers for Roche's drugs. "This screening is our window of opportunity to save lives and to help those who risk their lives to save others," Auble said. The firefighters tested will receive their results in about three weeks. Wednesday's session also included a one-hour education component with a slide show presentation and video on how to "protect yourself," while on the job.

Patients with Hepatitis C Using More Healthcare Resources

http://www.eurekalert.org/pub_releases/2005-11/jws-pwh112905.phpAging patient population burdens healthcare system

Chronic Hepatitis C virus (HCV) affects about 3 million people in the United States. Many patients contracted the disease in the 1970s before testing and safe needle-sharing practices were widespread. As this population ages, experts have predicted an increasing impact on the healthcare system. To understand how HCV outcomes are evolving, researchers, led by William C. Grant, Ph.D. of Duke University, analyzed hospitalizations, outpatient trends, and prescription drug data. They examined hospitalization trends for HCV-related and liver-related admissions from 1994 through 2001 using the Nationwide Inpatient Sample from the Healthcare Cost and Utilization Project. They tracked HCV-related physicians' visits from 1996 to 2002. They also gathered data on spending for interferon-ribavirin combination therapy between 1998 and 2000 from the Verispan Source Prescription Audit.

The researchers determined that HCV-related hospitalizations, hospital days, total charges, and deaths increased by more than 20 percent per year, three times higher than for all-cause hospitalizations. "The growth patterns were most striking for patients in their forties and fifties," the authors report. Patients in this age group spent more time in the hospital, incurred greater costs, and died more frequently than patients in other age groups. Physician office visits by HCV patients also increased by 36 percent each year. And spending on HCV drug therapy rose dramatically between 1998 and 2000, from \$78 per \$100,000 in new prescriptions to \$259. "The study documents accelerating use of healthcare resources by patients with HCV," the authors report, with average annual increases of 25 to 35 percent for the primary outcomes of interest, "indicating that the future burden of HCV infection will match and may exceed analysts' forecasts," they say. Their findings corroborate existing concerns over worsening health as HCV patients grow older.

The researchers also noted interesting disparities in HCV progression by gender, with slower disease progression among women. HIV-HCV co-infected patients, and children with HCV are two groups deserving further study. The authors performed sensitivity analyses to address the possibility of underreported HCV incidence, which remains an important limitation of this study. Still, they conclude, "our findings highlight the urgency concerning HCV outcomes. Across the United States, health care providers are using tremendous amounts of resources for HCV care. As patients continue to age and disease burden progresses, suboptimal decisions regarding HCV treatments will bring increasing opportunity costs for the health care system and society."

Hepatitis C Leadership Summit Engages HCV Stakeholders to Elevate the Response to the HCV Epidemic; New Opportunities for Action With Currently-Available Resources

http://www.genengnews.com/news/bnitem.aspx?name=1114637XSL_NEWSML_TO_NEWSML_WEB.xml

An estimated 4 million Americans have been infected by the hepatitis C virus (HCV). Because no significant new federal resources to fight the HCV epidemic are planned for the near future, improving on the current response requires creative and coordinated leveraging of available assets. The first annual Hepatitis C Leadership Summit (HCVLS) was convened on October 29-30, 2005 in Boston, to explore actionable opportunities to elevate the response to the HCV epidemic using currently identifiable resources.

Though there are certainly a wide array of issues that need attention, the HCVLS explored three specific areas of opportunity:

1. Engaging healthcare insurers, both private and public, on the opportunities available to cost-effectively respond to the HCV epidemic. Because inaction in the face of the epidemic will be vastly more expensive for insurers, a dialogue at the HCVLS engaged insurers in elevating HCV as a priority. Insurers can act as a primary motivator for the identification and treatment of those with hepatitis C, dramatically affecting the current response.
2. Producing better treatment results through a dissemination of physician best practices and care options for a broad array of patient types. The HCVLS also discussed the incorporation of adjunctive nutritional therapies to improve treatment compliance and outcomes, and the use of complementary therapies in conjunction with interferon or as an alternative.
3. Engaging community faith organizations to increase HCV Awareness (and thus testing and identification of HCV patients), and to provide support for those patients who have HCV whether or not they are receiving therapy.

"Based upon the feedback from participants, it's clear the HCVLS brought forth both new ideas and new opportunities for action," said Michael J. Russo, Partner at The Bruckner Group (BGI), and developer of the HCVLS concept. "There are a number of specific initiatives and new avenues to explore that are emerging from the HCVLS, and both the HARCP and BGI intend to follow through on them to the best of our abilities."

Attendees at the HCVLS included the majority of the State Hepatitis C coordinators, managed care payers, state Medicaid organizations, the CDC, academic and private practice clinicians, advocates, and pharmaceutical and biotechnology manufacturers. Senator Edward Kennedy (MA), who has taken the lead for more federal resources to fight the HCV epidemic, introduced the conference with a recorded video message welcoming participants and encouraging cross-stakeholder collaboration to produce heightened results. The HCVLS, initiated and organized by the Healthcare Advocacy and Research Collaboration Project (HARCP) and The Bruckner Group, was sponsored by Roche Pharmaceuticals and The Bruckner Group, with additional support from Schering-Plough Corporation, Valeant Pharmaceuticals International, and Vertex Pharmaceuticals.

Treatment of Genotype 1 Chronic Hepatitis C: Increased Sustained Virological Response with High-dose RBV and Epoetin

http://www.hivandhepatitis.com/2005icr/aasld/docs/112305_a.html

Anemia is the most important side effect of ribavirin (RBV), leading often to dose reductions and premature treatment discontinuations. RBV dose reductions also are associated with decreased SVR.

The use of epoetin (EPO) [Procrit] has been proven to reduce anemia and the need for RBV dose reductions. Study results presented at the 56th AASLD by Shiffman and colleagues show that the use of EPO also increases sustained virological response (SVR) when given with high doses of RBV to patients infected with HCV genotype 1. Naïve patients infected with HCV-1 were randomly assigned to one of three treatment groups:

Group 1: pegylated interferon (pegIFN)-a-2b (1.5 mg/Kg/week) + RBV 13.3 mg/Kg/day (N=48)

Group 2: pegylated interferon (pegIFN)-a-2b (1.5 mg/Kg/week) + RBV 13.3 mg/Kg/day + EPO (N=49)

Group 3: pegylated interferon (pegIFN)-a-2b (1.5 mg/Kg/week) and RBV 15.2 mg/Kg/day +EPO (N=49)

In groups 2 and 3, EPO was given at onset of treatment if hemoglobin values were < 15 g/dL, or later on as soon as hemoglobin levels dropped below that threshold. EPO dose was initially 40,000 U/week, and doses were increased to 60,000 U/week if no response was obtained.

Groups were similar in age (median 48 years), proportion of African Americans (36-43%) and body weight (median 82.4 Kg). Only a minority of patients had cirrhosis, and although without statistically significant differences, it was more common in group 2 (8%) than in groups 1 (4%) and 3 (2%).

The table summarizes the results of the study:

	Group 1 RBV 13.3/kg	Group 2 RBV 13.3/kg+EPO	Group 3 RBV 15.2/kg+EPO
EVR	67%	53%	65%
ETR	48%	46%	55%
SVR	27%	24%	45%*
Relapses**	36%	40%	8%*
% RBV dose reduction	40%	10%***	31%
D/C anemia	4%	2%	0%
Hb <10g/dL	34%	9%	6%
Hb <8.5 g/dL	2%	2%	0%

* p<0.05 vs. groups 1 and 2

** % of responders at the end of treatment

*** p<0.05 vs. group 1

D/C: discontinuations

No significant differences were found in early virological response (EVR) or end-of-treatment response (ETR), but there were less relapses and higher proportion of SVR in the high RBV dose group compared to the others. SVR were higher in the high RBV dose group than in the other groups regardless of race (African-American, 31% vs. 18%; non-African American, 53% vs. 30%). In summary, the use of EPO significantly decreased the frequency of anemia, and the need for RBV dose reductions and premature discontinuations. The use of higher doses of RBV (1,000-1,600 mg/day) decreased relapses and therefore increased SVR across all body weights and races in patients infected with HCV genotype 1.

These results are encouraging and suggest that the use of high doses of RBV should be evaluated in large clinical trials.

Reference: M L Shiffman, et al. Treatment of chronic hepatitis C virus (HCV) genotype 1 with peginterferon alfa-2b (PEGIFN), high weight based dose ribavirin (RVN) and epoetin alfa (EPO) enhances sustained virologic response (SVR). Abstract 55. 56th annual meeting of the American Association for the Study of Liver Diseases (56th AASLD). November 11-15, 2005. San Francisco, CA.

Efficacy of Daily Consensus Interferon (Infergen) and Ribavirin Compared to PEG-Interferon Alfa-2b (PegIntron) and Ribavirin in Nonresponders with Chronic Hepatitis C

http://www.hivandhepatitis.com/2005icr/aasld/docs/112805_f.html

Consensus interferon/CIFN (Infergen) is a synthetic interferon that demonstrates enhanced potency in laboratory studies compared to conventional interferon alfa. In the present prospective, randomized, multicentre trial, researchers at the Martin-Luther-University Halle-Wittenberg, in Halle, Germany evaluated the efficacy, tolerability and safety of consensus interferon (CIFN) *daily* versus pegylated IFN a-2b (PEG-IFN) (PegIntron) *once weekly* in combination with ribavirin (RBV) for HCV non-responders to previous combination treatment with IFN and RBV.

Forty patients with histologically proven chronic hepatitis C, who were HCV RNA positive, had elevated transaminases and previous non-response to treatment with combination therapy with IFN and RBV were randomised to 18 mcg/D CIFN for 6 weeks followed by 9 mcg/D CIFN for 42 weeks (CIFN + RBV: 18 patients) or 1.5 mcg/kg body weight of PEG-Interferon α -2b once a week for 48 weeks (PEG-IFN + RBV: 22 patients), each in combination with RBV (> 10.6 mg/kg body weight daily). There were no statistical differences between the two groups regarding sex, age, weight, or presence of cirrhosis. All study participants patients had HCV genotype 1b.

Based on an intent-to-treat analysis, the early response rate (ER, 24 weeks of treatment), the end-of-treatment response rate (ETR, 52 weeks of treatment) and the sustained response rate (SR, 6 months after treatment) are reported in Table 1. No significant difference was detected between the two groups.

Table 1: Biochemical and Virological Response

	ER	ETR	SR
CIFN + RBV	7/18 (39%)	7/18 (39%)	4/18 (22%)
PEG IFN + RBV	8/22 (27%)	6/22 (27%)	5/22 (23%)

- There was no clinically significant difference in the incidence of adverse events between the two groups.
- However, there was a significant higher number of patients withdrawing within the first 6 months from CIFN + RBV than from PEG-IFN because of subjective side-effects (6/18 vs. 1/22, $p < 0.05$, **Figure 1**).
- In contrast, the treatment was terminated because of primary non-response after 6 months in 8/22 patients treated with PEG-IFN + RBV versus only 2/18 patients treated with CIFN + RBV ($p < 0.05$).
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The German authors conclude, “Based on an intent-to-treat analysis, daily CIFN combined with ribavirin has the same antiviral efficacy and safety profile for the treatment of non-responders with chronic hepatitis C as weight adjusted peg-IFNa2b (PegIntron). The daily regimen of CIFN is, however, less well tolerated by patients. A potential higher efficacy can therefore not be established in studies, and will be difficult or impossible to achieve outside of studies.”

Reference: M M Dollinger, et al. Efficacy of Daily Consensus Interferon and Ribavirin Compared to PEG-Interferon α -2b and Ribavirin in Non-Responders with chronic Hepatitis C. Abstract 1253. 56th annual meeting of the American Association for the Study of Liver Diseases. November 11-15, 2005. San Francisco, CA.

Consensus Interferon (Infergen) and Ribavirin in Nonresponders to Prior Therapy with Either Standard Interferon Alfa and Ribavirin or Pegylated Interferon and Ribavirin

http://www.hivandhepatitis.com/2005icr/aasld/docs/112805_d.html

Currently, there are no FDA-approved treatment options for individuals who fail to achieve a sustained virological response (SVR) to the standard of care—peginterferon plus ribavirin combination therapy. In the present review, investigators at 3 midwestern medical centers describe their experience using consensus interferon (CIFN) (Infergen) [aka interferon alfacon-1] plus ribavirin (RBV) in nonresponders (NR) to peginterferon + ribavirin.

All patients were treated initially with IFN alfa-2a (Pegasys) monotherapy or Peg IFN + RBV. Those who failed to achieve undetectable HCV RNA were classified as NR and were then retreated with CIFN + weight-based RBV (800 mg-1200 mg/day) for at least 48 weeks. Pretreatment liver biopsy, HCV genotype, viral load and various demographic information were collected for all subjects. Patients on CIFN + RBV retreatment were allowed to use growth factors to continue with their treatment on an as needed basis. All patients received CIFN at a starting dose of 15 mcg/daily with weight-based RBV. Doses were adjusted as necessary for hematological side effects.

Results

- 79 patients were screened and 76 patients were treated with CIFN and RBV (65% Caucasian, 16% African American, 4% Hispanic, 15% other);
- 49 male and 27 female; age ranged from 20-76 years (Mean: 61 (80%) had HCV genotype 1;
- 36 (47%) had Metavir fibrosis F3/F4.
- At the end of treatment (week 48), 55 (72%) patients were HCV RNA negative.
- At week 72, 38 (50%) achieved an SVR.
- One patient on treatment underwent liver transplantation and stopped treatment. At that time, his viral load had dropped to 1,830 copies/mL.

	Week 48 (end of treatment)	Week 72 (SVR)
HCV RNA negative	55 (72%)	38 (50%)

According to the authors, “These data suggest that IFN alfacon-1 and weight-based RBV are a potential alternative in Peg IFN plus RBV NR HCV patients. In addition, NR patients with advanced disease (F3/F4) tolerated this therapy well and should be candidates for retreatment with IFN alfacon-1 and RBV. Further study is warranted to confirm these findings.”

Reference: K Chen, et al. Consensus interferon and ribavirin in patients with chronic hepatitis C who were nonresponders to prior therapy with either interferon alfa and ribavirin or pegylated interferon and ribavirin. Abstract 1203. 56th annual meeting of the American Association for the Study of Liver Diseases. November 11-15, 2005. San Francisco, CA.

Sustained Virologic Response Rates from a Randomized Trial of HCV Genotype-1 Subjects Treated with Either Consensus IFN and Ribavirin or Pegylated Interferon alfa-2b and Ribavirin

http://www.hivandhepatitis.com/2005icr/aasld/docs/112805_c.html

It is well known that greater than 50% of HCV genotype 1 individuals treated with the standard of care, peginterferon alfa plus ribavirin, fail to achieve a sustained virological response (SVR). Results of a few studies suggest that consensus interferon (CIFN) (Infergen) in combination with ribavirin (RBV) may be particularly active against HCV genotype 1 and therefore might improve SVR rates in this patient population.

In the current study, researchers at multiple US medical centers sought to evaluate the effects of treatment with proof of concept study to compare treatment with CIFN/RBV to pegylated interferon (PEGIFN) and

RBV in achieving SVR. In this prospective, randomized clinical trial, treatment-naïve HCV genotype-1 patients received either CIFN 15 mcg TIW and weight-based generic ribavirin (Ribasphere) (**group 1**) or PEG-Intron 1.5 mcg/kg/week and weight based ribavirin (Rebetol), (**group 2**). Fifty-nine individuals were enrolled, 30 in group 1 and 29 in group 2. Treatment lasted 48 weeks if HCV RNA was undetectable at week 24, otherwise drugs were discontinued. SVR was determined at week 72. Safety laboratory tests and adverse events (AE) assessments were performed monthly. To date all subjects have completed week 48 and 56 subjects have finished week 72.

Results

- At baseline the 2 groups were similar in gender (67% men), age (mean = 44 years), weight (202 lbs men, 152 lbs women), ethnicity (59% Caucasian, 30% African American), high viral load (75%, mean levels: 3.8 and 3.6 million IU/mL for groups 1 and 2) and hemoglobin (mean: 15 g/dL).
- Cirrhosis was diagnosed in 3 subjects in group 1 and 5 subjects in group 2. The SVR was similar for both groups: 37% for CIFN/RBV and 35% for PEGIFN/RBV.
- No subject dropped hemoglobin to <8.5 g/dL. Neutrophils dropped to <750/uL in 13% and 24% of groups 1 and 2, respectively (p= 0.29).
- Dose modification for one or two drugs were required in 37% and 62% in each of the 2 groups (p=0.09).
- AE were flu-like symptoms in 100% and 93%, headache in 63% and 39%, fatigue in 77% and 50%, mood disorders in 67% and 66%.
- Serious AE were observed in 6 subjects (3 per group) (cellulitis, severe fatigue, psychosis, seizure, dehydration, EtOH recidivism, and pyelonephritis).

Based on these results, the study authors conclude, “CIFN/RBV combination therapy elicited a comparable SVR to PEGIFN/RBV in previously untreated subjects with genotype-1 chronic HCV. There were no relapsers among the CIFN/RBV treated group. The AE profile for CIFN/RBV demonstrated less neutropenia and dose reductions. A larger clinical trial for genotype-1 chronic HCV infection utilizing CIFN and ribavirin is warranted.”

Reference: M Sjogren and others. Sustained Virologic Response Rates from a Randomized Trial of HCV Genotype-1 Subjects Treated with Either Consensus IFN and Ribavirin or Pegylated Interferon alfa-2b and Ribavirin. Abstract 851. 56th annual meeting of the American Association for the Study of Liver Diseases. November 11-15, 2005. San Francisco, CA.

Hepatitis C: The Uncounted Disease

<http://www.nhpr.org/node/9845>

Hepatitis C is the most common blood borne infection in the United States. And it's the leading cause of liver transplants. About three million people are walking around with the virus and according to the Centers for Disease Control, most of them are completely unaware that they are infected.

Hepatitis C often hides in the body for two or more decades before it becomes life threatening. And it is very unpredictable. Only one out of four people with a chronic infection is likely to develop the most serious liver diseases. New Hampshire Public Radio has found evidence of a building wave of Hepatitis C hitting the state's health care system. But unlike many other infectious disease, the state does not track Hepatitis C and does not require doctors to report when they find patients who carry it.

ViroPharma Announces That Treatment With HCV-796 Reduces Hepatitis C Virus Levels

<http://www.primezone.com/newsroom/news.html?d=89526>

ViroPharma Incorporated today announced preliminary results from a Phase 1b proof of concept study with HCV-796, an orally dosed hepatitis C (HCV) viral polymerase inhibitor with the potential to interfere with the replication of hepatitis C virus, that is being co-developed with Wyeth Pharmaceuticals,

a division of Wyeth. In this trial, HCV-796 demonstrated antiviral effects in adult patients with chronic hepatitis C infection. The patient cohort with the highest exposure to HCV-796 achieved a peak mean HCV viral load reduction of 1.4 log₁₀, or 96 percent, on day four of a 14 day dosing period. HCV-796 was found to be generally well tolerated, with favorable pharmacokinetics and no dose-limiting toxicities.

"Hepatitis C is a devastating disease, and a difficult target for anti-viral medicines. With our partners at Wyeth, we have now demonstrated anti-HCV activity with HCV-796, the only non-nucleoside polymerase inhibitor to have positive clinical antiviral data," commented Colin Broom, ViroPharma's chief scientific officer. "This potentially opens up new treatment possibilities for patients suffering from the disease. These new data suggest that HCV-796 has a good tolerability profile, favorable pharmacokinetics, and the potential to improve on the level of virologic response across multiple HCV genotypes, including genotype 1, which is the most common strain in the U.S. and the least responsive to currently available therapies. In the future, as antiviral compounds become available, patients suffering with hepatitis C will likely be treated with various combination therapies, analogous to the treatment paradigm for HIV infected patients."

The Phase 1b proof of concept study was a randomized, double blind, placebo-controlled study of HCV-796 administered orally for 14 days to patients with chronic HCV infection who were naive to treatment. Patients were enrolled in sequential, ascending-dose cohorts of up to 16 patients (12 receiving HCV-796 and 4 receiving placebo) per cohort. Inclusion criteria in this trial include documented history of HCV infection for greater than 6 months, and HCV RNA levels of greater than 104 IU/mL at the screening evaluation. Subjects were permitted to participate in only 1 cohort. The trial was conducted at a single U.S. site. The objectives of this trial were to compare the safety and tolerability of ascending multiple oral doses of HCV-796 with those of a placebo in subjects with chronic HCV infection, to characterize the pharmacokinetic profile of multiple oral doses of HCV-796, and to compare the antiviral effect of HCV-796 with that of a placebo on plasma HCV RNA concentrations.

Preliminary results are available for patients in six cohorts (twice-daily oral administration of 50, 100, 250, 500, 1000, and 1500 mg). Seventy two percent of all patients were infected with HCV genotype 1. HCV-796 was generally well tolerated across the treatment groups, and no dose-limiting toxicity was identified. Mild to moderate headache was the most frequent adverse event reported overall. There were no treatment-emergent serious adverse events. A single patient withdrew from each of the top three cohorts due to non-serious adverse events, two were considered possibly related to therapy (bilirubin elevation and TSH elevation) and the other considered non-related to therapy (loss of hypertension control).

HCV-796 exhibited favorable pharmacokinetics with an estimated mean elimination half-life of 42-54 hours across dose groups. HCV-796 drug levels increased less than proportionally with increasing dose, and appeared to reach a plateau at the 1000 mg cohort. Through the first five cohorts, dose related responses to HCV-796 as measured by reduction in plasma HCV RNA levels were observed. In the 1000 mg cohort, the mean reduction in HCV RNA was 1.4 log₁₀ (96 percent) on day four, 1.3 log₁₀ (95 percent) on day seven, and 0.7 log₁₀ (80 percent) at day 14. At day four, 83 percent of patients in this cohort had reductions from baseline greater than 1.0 log₁₀ on day four; 33 percent of these subjects had reductions greater than 1.5 log₁₀; 25 percent of these subjects had reductions greater than 2.0 log₁₀. On day 14, 17 percent of subjects in this group had reductions from baseline greater than 2.0 log₁₀.

Viral reduction curves were of a similar pattern across all cohorts. Maximal antiviral effects were observed at approximately study day four, when peak mean reductions in HCV RNA ranged from 0.3 to 1.4 log₁₀ (50 to 96 percent) across all doses. At day seven of treatment, mean HCV RNA levels were 0.3 to 1.3 log₁₀ (50 to 95 percent) below baseline. At day 14 of treatment, mean HCV RNA levels were 0.2 to 0.7 log₁₀ (37 to 80 percent) below baseline. For patients receiving placebo, mean plasma HCV RNA

increased 0.1 log₁₀ compared to baseline on day four, and was unchanged from baseline on day 14. Antiviral activity appeared similar among patients infected with HCV genotype 1 compared to those with non-genotype 1 infection, although fewer subjects were infected with non-genotype 1 HCV. Further analysis, including pharmacodynamic/pharmacokinetic correlation and viral genetic sequencing, is planned.

ViroPharma and Wyeth plan to assess the antiviral activity, pharmacokinetics and tolerability of HCV-796 in combination with pegylated interferon. These data are expected at the beginning of the second quarter of 2006. If these data are supportive, the companies will determine the next steps, including progression to a Phase 2 study.

Hepatitis C Often Untreated and Outcomes Lag behind Trials in Clinical Practice

<http://www.docguide.com/news/content.nsf/news/8525697700573E18852570B400490056>

When patients with hepatitis C go on antiviral therapy, the likelihood of a response may be half of that seen in clinical trials, according to investigators who presented their findings here at the 70th annual meeting of the American College of Gastroenterology (ACG). The research was presented on November 2nd by Ramsey C. Cheung, MD, Chief of Hepatology, Veterans Affairs Palo Alto Health Care System, and Associate Professor of Medicine, Stanford University Medical School, Stanford, California, United States.

"A lot of people with a diagnosis of hepatitis C are not being treated for multiple reasons," Dr. Cheung, MD, said in an email. "When we decide to treat a patient and when the patient decides to go on treatment, the probability of achieving a cure is important to both parties." However, he added, his study showed that the response rate is much lower in clinical practice than has been seen in the registration trial. "It is important for the treating physician and the patient to know what the response rate is likely to be, not what has been reported in registration trial." He noted that studies of patients with hepatitis C within the Veterans Affairs system showed that the sustained viral response rate was low. The investigative team conducted the current study to see if the same results would be seen in a community cohort.

The team reviewed several databases of selected sites within the Kaiser Permanente Northern California Health System, and identified 1470 patients with chronic hepatitis C who were seen within the system from 1999-2004. They obtained demographic information from administrative files on age, gender, and ethnicity and patients' laboratory records. The system's pharmacy records held data on patients' treatment with interferon combined with ribavirin or pegylated interferon combined with ribavirin, along with information regarding the patients' use of erythropoietin (Procrit), filgrastim (Neupogen), antidepressants, and transfusions.

Results show that 246 (16.5%) underwent treatment; 65.3% of these patients were men. Data were completely evaluable for 242 patients; 119 of these were treated with interferon plus ribavirin, and 123 were treated with pegylated interferon plus ribavirin. Patients were an average of 47.1 years old (range 33.3-60.91). The vast majority of treated patients (72.4%) had HCV genotype I, while 24% had HCV genotypes II and III, and 3.6% had HCCV genotypes IV-VI. Patients were treated for an average of 29.2 weeks. A sustained virologic response occurred in 19.8% of treated patients, including 11.8% of those who received interferon plus ribavirin, and 27.6% of those treated with pegylated interferon plus ribavirin. In clinical trials, sustained viral response rates have reached more than 70%, Dr. Cheung said.

Although the reasons for the gap are unclear, these findings may help physicians, and patients have more realistic expectations of treatment, Dr. Cheung said.

Relatives of Hepatitis C Victims Who Died after Receiving Blood Transfusions have Launched a Legal Action to Seek a Public Inquiry into the Deaths. [UK]

<http://www.eveningtimes.co.uk/hi/news/5045712.html>

Lawyers acting for the three people yesterday urged a judge to take the unusual step in Scots law of making protective costs orders in the cases - to limit their liability in the event of failure - to let their fight for justice go on. Aidan O'Neill QC told the Court of Session in Edinburgh: "They are all quite clear they would not be able to proceed if they were exposed to the risk of having to pay such substantial sums of money." The court was told that since 1980, 4000 people have been infected with Hepatitis C virus after receiving blood products while under the care of the NHS in Scotland. Neil Davidson QC, for the Executive, asked Lord Glennie to report the case to a bench of three judges to consider the expenses order if it was to be brought into Scots law. The judge reserved his decision.

Los Angeles Summit Focuses on Fighting Hepatitis C

http://www.advocate.com/news_detail_ektid22839.asp

Health officials gathered in Los Angeles recently to discuss the region's successes—and failures—in fighting the spread of hepatitis C, California's KPCC News radio reports. Stephen Simon, AIDS coordinator for the city of Los Angeles, said county officials, the state of California, and the federal government all are falling far short in their efforts to combat the blood-borne disease, which can be spread through certain sexual practices and is a common coinfection among HIV patients.

As many as 650,000 Californians carry the hepatitis C virus; nationwide, there are an estimated 5 million HCV cases. Some researchers have estimated that up to 25% of HIV patients are also coinfecting with HCV, with the coinfection rate rising to as high as 50% of all HIV-positive injection-drug users. A study in the American Journal of Public Health says that if health leaders don't make significant strides in crafting HCV education and prevention programs, there could be nearly 200,000 U.S. deaths from the disease by 2019 and nearly \$11 billion in health care costs.

Among the topics discussed at the Los Angeles summit were providing hepatitis treatment to prisoners, reaching the homeless with HCV awareness and prevention outreach, and helping to prevent infections among injection-drug users, who often put themselves at high risk for the blood-borne disease by sharing needles. Sexually active gay men are at a high risk for contracting hepatitis and are urged to be vaccinated against hepatitis A and B. There currently is no vaccine for hepatitis C.

Woman Sues Board of Education Over Hepatitis C Infection

<http://www.theepochtimes.com/news/5-11-16/34648.html>

After getting infected with Hepatitis C, a paraprofessional from the city's public school system is suing the Board of Education for failing to provide her with adequate education about and protection from the disease. Laurie Baron, who works with "special needs" children, was diagnosed with Hepatitis C in November 2003. She claims that she was infected from repeatedly coming into contact with the blood and feces of the children under her care.

"The students are wonderful," Baron told members of the press on Nov. 15, "but some of them self-mutilate, some bite, some are very aggressive as part of their special condition."

Her sickness has caused her to endure, "48 weeks of grueling treatment." Also, she was out of work for over five months, for which she received no pay. United Federation of Teachers (UFT) president Randi Weingarten stressed that it was the school's responsibility to follow protocols meant to protect the children and staff. "There are standards about how to deal with blood, and the Board of Education routinely ignores these standards, and as a result, both the staff and sometimes children have become sick," she said. Weingarten went on to explain that, "Educators are not being offered vaccines or being adequately trained. In most cases they get very little equipment—maybe a pair of latex gloves."

Department of Education guidelines call for vaccinations as well as training and the use of protective measures when dealing with the possible transmission of blood-borne pathogens. All schools are required to comply with the Blood Born Pathogen Standard, a federal law enforced by Occupational Safety and Health Administration. After Barron's diagnosis, the Public Employee Safety and Health Bureau conducted an investigation and found her school guilty of 14 violations, for which the Board of Education was fined tens of thousands of dollars.

The board asserts that it has practices in place, such as the use of gloves that should protect employees, but Baron claimed, "We were told directly that there were not enough gloves, so please use them sparingly. Or, we were told not to use them at all, because they make the children feel bad." Lou Heller, the chief attorney representing Baron's case, said that his client is simply demanding that the Board of Education admit its negligence and take the necessary steps to right the situation. "Correct the problem. Workers' compensation doesn't cure Hepatitis C," said Heller.

Largest Hepatitis C Trial in U.S. Patients Shows Weight-Based REBETOL in Combination With PEG-INTRON Increases Sustained Response, Lowers Relapse - Final Results of Community-Based WIN-R Study Also Demonstrate Efficacy of Shorter, More Tolerable 24-Week Regimen in Patients With Genotype 2 or 3 Virus

http://www.marketwire.com/mw/release_html_b1?release_id=101076

Final results of the WIN-R trial,(1) the largest hepatitis C study conducted in U.S. patients, showed that weight-based REBETOL® (ribavirin, USP) in combination therapy with PEG-INTRON® (peginterferon alfa-2b) achieved significantly higher rates of sustained virologic response (SVR)(2) and lower rates of relapse compared to the combination therapy using a flat dose of ribavirin. The study also showed that, for patients infected with hepatitis C virus (HCV) genotype 2 or 3, a shorter, 24-week course of therapy was as effective as the standard 48-week course, with better tolerability.

These results from WIN-R (Weight-Based Dosing of PEG-INTRON and REBETOL), a community-based access trial involving more than 4,900 patients at 225 centers across the United States, were reported in an oral presentation today at the 56th annual meeting of the American Association for the Study of Liver Diseases (AASLD). "These findings help further define optimal therapy for U.S. hepatitis C patients treated in real-world community settings," said principal investigator Ira M. Jacobson, M.D., Vincent Astor Professor of Clinical Medicine at Weill Medical College of Cornell University and chief of the division of gastroenterology and hepatology at New York-Presbyterian Hospital/Weill Cornell Medical Center in New York City.

Treating U.S. hepatitis C patients can be especially challenging as they tend to have disease characteristics that are associated with poor response to treatment, including high prevalence of HCV genotype 1, the most difficult type of the virus to treat; high viral load; and advanced liver fibrosis. Other factors such as age, high body weight and African-American ethnicity also have been shown to be associated with poor response.

"Our findings showed that the weight-based dosed combination therapy significantly increased efficacy compared to the flat-dosed ribavirin regimen, especially in more difficult-to-treat patient groups, such as patients with genotype 1 and African-American patients. This confirms what many treating physicians have come to know in their everyday practice and experience," Jacobson said. "Importantly, sustained virologic response rates in this community-based U.S. study were consistent with those seen in the U.S. cohorts of the earlier pivotal studies for the two approved peginterferon combination therapies."

In the WIN-R study, 4,913 patients were randomized to receive weight-based PEG-INTRON (1.5 mcg/kg weekly) in combination with REBETOL given either as a flat dose (800 mg daily) or a weight-based dose (800 mg, 1,000 mg, 1,200 mg or 1,400 mg daily for body weights of less than 65 kg, 65 to 85 kg, 86 to

105 kg, or 106 to 125 kg, respectively). Patients were treated for 48 weeks (genotype 1) or 24 weeks (genotype 2 or 3). Patients in the treatment arms were evenly matched for gender, age, body weight, genotype, viral load and stage of liver fibrosis.

...In the WIN-R study, 13.1 percent (164/1,256) of patients in the weight-based dose group and 13.7 percent (163/1,193) of patients in the fixed-dose group who were responders at the end of treatment were lost to follow up and subsequently counted as treatment failures under a strict intent-to-treat (ITT) analysis. Nonetheless, the WIN-R study showed significantly better outcomes for the weight-based combination regimen as compared to the flat-dosed ribavirin regimen, including:

- Significantly higher SVR overall (44.3 percent vs. 40.6 percent, $p=0.01$, ITT) and for patients with genotype 1 (34 percent vs. 29 percent, $p=0.004$, ITT). These SVR rates are consistent with those seen in the U.S. cohorts of the earlier pivotal studies for the two approved peginterferon combination therapies.
- Using an estimated SVR analysis, based on results for patients who had undetectable virus at the end of treatment and were subsequently lost to follow up, SVR was 53 percent vs. 48 percent ($p=0.008$), respectively, for the weight-based vs. flat-dosed ribavirin groups.
- Consistent SVR rates were seen across all weight groups for patients in the weight-based dosed regimen compared to the flat-dosed ribavirin regimen where SVR rates declined in the higher weight groups, ranging from 52 percent to 34 percent. Consistent with other U.S. studies, patient weight tended to be high in the WIN-R study, with 45 percent of patients weighing 86 kg (189 lbs) or more.
- For patients with HCV genotype 2 or 3 virus, a 24-week course of the combination therapy was as effective as 48 weeks, with better tolerability. In the weight-based dose arms, SVR was 68 percent for the 24-week course compared to 60 percent for the 48-week course, with the lower percentage attributable to more missing follow-up data.
- Lower rates of relapse were seen for patients receiving the weight-based combination therapy compared to the flat-dosed ribavirin regimen, 15 percent vs. 19 percent overall, and 23 percent vs. 29 percent for patients with HCV genotype 1.
- Although there was a higher rate of anemia (hemoglobin < 10 gm/dl) in the weight-based dosing group and more dose reductions (29 percent vs. 23 percent), no difference was seen in the rate of occurrence of serious adverse events between the two groups (12 percent vs. 11 percent) and there were similar rates of discontinuations for adverse events (15 percent vs. 14 percent).

CLINICAL TRIALS, COHORT STUDIES, AND PILOT STUDIES

Non-response to antiviral therapy is associated with obesity and increased hepatic expression of SOCS-3 in patients with chronic hepatitis C, viral genotype 1. Walsh MJ, et al. Gut. 2005 Nov 18; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16299039&query_hl=5

INTRODUCTION: Interferon-alpha (IFN) -activated cellular signalling is negatively regulated by inhibitory factors including the suppressor of cytokine signalling (SOCS) family. The effects of host factors such as obesity on the hepatic expression of these inhibitory factors in subjects with chronic HCV are unknown. **OBJECTIVES:** To assess the independent effects of obesity, insulin resistance (IR) and steatosis on response to IFN therapy and to determine the hepatic expression of factors inhibiting IFN signalling in obese and non-obese subjects with chronic HCV. **METHODS:** 145 subjects were analysed to determine host factors associated with non-response to antiviral therapy. Treatment comprised IFN or peginterferon-alpha either alone or in combination with ribavirin. In a separate cohort of 73 patients, real time (RT)-PCR was performed to analyse hepatic mRNA expression. Immunohistochemistry for SOCS-3

was performed on liver biopsy samples from 38 patients with viral genotype 1 who had received antiviral treatment. **RESULTS:** Non-response (NR) to treatment occurred in 55% of patients with HCV genotypes 1 or 4 and 22% with genotypes 2 or 3. Factors independently associated with NR were viral genotype 1/4 ($p < 0.001$), cirrhosis on pre-treatment biopsy ($p = 0.025$) and BMI $\geq 30 \text{ kg/m}^2$ ($p = 0.010$). Obese subjects with viral genotype 1 had increased hepatic mRNA expression of PEPCK ($p = 0.01$) and SOCS-3 ($p = 0.047$), in comparison with lean subjects. Following multivariate analysis, SOCS-3 mRNA expression remained independently associated with obesity ($p = 0.023$). SOCS-3 immunoreactivity was significantly increased in obesity ($p = 0.013$) and in NR compared with responders ($p = 0.014$). **CONCLUSIONS:** In patients with chronic HCV viral genotype 1, increased expression of factors that inhibit interferon signalling may be one mechanism by which obesity reduces the biologic response to IFN.

Prospective study on early virologic response to treatment with interferon alpha-2b plus ribavirin in patients with chronic hepatitis C genotype 1b. Nagaki M, et al. *Hepatol Res.* 2005 Nov 16; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16298546&query_hl=5

To evaluate the predictive value of early virologic response (EVR) of achieving a sustained virologic response (SVR), an open, prospective trial including 42 patients with chronic hepatitis C genotype 1b was performed with directly observed 24-week treatment with interferon alpha-2b plus ribavirin. We assessed the predictive values of EVR at days 3, 7, 14, and weeks 4, 8, and 12 of the SVR. The SVR in an intention-to-treat analysis was 19.0%. Patients who reached SVR presented a significantly faster reduction in plasma viral load. Stepwise multiple logistic regression analysis of the factors (gender, age, IFN dosage, ribavirin dosage, HCV RNA, ISDR, and loss of HCV RNA at week 4) revealed that loss of HCV RNA at week 4 was the only independent variable of treatment outcome ($P = 0.0039$). A viral load at treatment day 3 above 100kIU/ml, at day 7 above 50kIU/ml, and at day 14 above 10kIU/ml was 100% predictive for virologic non-response in all except 1 patient. The cutoff levels for HCV RNA at days 3 and 14 of treatment were associated with an algorithm of the failure to detect HCV RNA after 12 weeks of treatment. **In conclusion**, a very early virologic response assessment could be useful for prediction of later outcome of combination therapy in chronic hepatitis C genotype 1b.

Digestive endoscopy and HCV transmission. Bronowicki JP. *J Hepatol.* 2005 Nov 15; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16297491&query_hl=5

BACKGROUND: The potential role of digestive endoscopy as a mode for transmission of hepatitis C virus (HCV) is controversial. **OBJECTIVE:** To evaluate the role of digestive endoscopy in transmitting HCV by comparing the incidence of HCV infection in a cohort of patients undergoing endoscopy and in a cohort of blood donors. **DESIGN:** Prospective cohort study. **SETTING:** Three endoscopic units and two blood banks in northwestern Italy. **PATIENTS:** The potentially exposed cohort consisted of 9188 outpatients consecutively recruited from three endoscopic units. Of 9008 patients negative for antibody to HCV (anti-HCV), 8260 (92%) were retested for anti-HCV 6 months after endoscopy. The unexposed cohort consisted of 51,230 healthy, anti-HCV-negative persons who donated blood at two blood banks in the same area and during the same time period; 38,280 of them (75%) were tested again for anti-HCV 6-48 months after the first blood donation (95,317 person-years of observation). **MEASUREMENTS:** Differences in the anti-HCV seroconversion rate between the exposed cohort (patients undergoing endoscopy) and the unexposed cohort (blood donors). Seroconversion was evaluated by a third-generation enzyme immunoassay for anti-HCV; persons positive for anti-HCV were tested for HCV RNA by polymerase chain reaction. **RESULTS:** All 8260 persons undergoing endoscopy remained negative for anti-HCV 6 months after the procedure (risk per 1000 persons, 0 [95% CI, 0-0.465]); in particular, none of the 912 patients who underwent endoscopy with the same instrument previously used on HCV carriers showed anti-HCV seroconversion (risk per 1000 persons, 0 [CI, 0-4.195]). Four blood donors became

positive for anti-HCV and HCV RNA (mean follow-up, 2.49 years; 0.042 case per 1000 person-years [CI, 0.011-0.107 case per 1000 person-years]); each had undergone minor surgery before the second test
LIMITATIONS: In the endoscopy cohort, 8.3% of patients were lost to follow-up. **CONCLUSIONS:** These findings support the hypothesis that properly performed digestive endoscopy is not a major risk factor for the transmission of HCV. [Abstract reproduced by permission of Ann Intern Med 2005;142: 903-909].

Efficacy of 24 weeks treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C infected with genotype 1 and low pretreatment viremia. Zeuzem S, et al. J Hepatol. 2005 Nov 7; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16290907&query_hl=5

BACKGROUND/AIMS: Previous studies using standard interferon and ribavirin combination therapy suggested that patients infected with HCV-1 and a low pretreatment HCV-RNA level can be treated for 24 weeks without compromising sustained virologic response rates. The aim of the present study was to investigate this schedule in the era of pegylated interferon-alpha plus ribavirin. **METHODS:** Patients chronically infected with HCV-1 (n=235) and a screening viremia \leq 600,000IU/mL (real-time PCR) were treated with peginterferon alfa-2b 1.5mg/kg subcutaneously once weekly plus ribavirin 800-1400mg/day based on body weight for 24 weeks. **RESULTS:** End-of-treatment and sustained virologic response rates were 80 and 50%, respectively. The 48-week historical control (Manns et al., Lancet 2001;358:958-65) had similar end-of-treatment (74%) but higher sustained virologic response rates (71%). This difference was due to a high virologic relapse rate after 24 weeks of therapy (37%) compared with the historical control (4%). A subset of patients who had undetectable serum HCV-RNA at treatment week 4, however, achieved similar sustained virologic response rate (89%) as in the control group (85%). **CONCLUSIONS:** HCV-1 infected patients with a low baseline HCV-RNA concentration who become HCV-RNA negative at week 4 may be treated for 24 weeks without compromising sustained virologic response rates.

Clearance of HCV RNA in peripheral blood mononuclear cell as a predictor of response to antiviral therapy in patients with chronic hepatitis C. Xu DZ, Xie Y, Li ZQ. Hepatobiliary Pancreat Dis Int. 2005 Nov;4(4):550-3.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16286260&query_hl=5

BACKGROUND: The resolution of hepatitis C, evidenced by normalization of liver function and disappearance of hepatitis C virus RNA from serum as determined by conventional laboratory assays, reflects virus eradication. But in interferon treated patients the HCV RNA in serum sometimes could not show the virus in cells. Such factors as virus genotype, HCV RNA contents in serum, HCV specific cellular immunities after treatment were reported to predict the response to interferon therapy. In most patients, HCV RNA could detect the virus in peripheral blood mononuclear cell. The aim of this study was to investigate the predictive value of HCV RNA in PBMC of patients with chronic hepatitis C after interferon treatment. **METHODS:** Sixteen patients with chronic hepatitis C were treated with interferon for 24 weeks, and they all get complete responses at 12 weeks of treatment. At the end of treatment, the HCV RNA in PBMC and serum were detected by RT-PCR, and after stopping treatment, HCV RNA in serum was monitored continually. **RESULTS:** In 9 patients who were HCV RNA positive in their PBMC at the end of treatment, 8 showed serum HCV RNA positive after 24 weeks and another 1 after 1 year. In 7 patients with negative HCV RNA in their PBMC, only 2 patients relapsed in serum HCV RNA after 1-year follow-up, and others remained viral response after 3.5 years. **CONCLUSION:** HCV RNA in PBMC at the end of IFN treatment is a predictor of durable response to antiviral therapy in patients with chronic hepatitis C.

A randomized trial of pegylated interferon alpha-2b plus ribavirin in the retreatment of chronic

hepatitis C. Jacobson IM, et al. Am J Gastroenterol. 2005 Nov;100(11):2453-62.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16279900&query_hl=5

OBJECTIVES: The efficacy of combination therapy with pegylated interferon (PEG IFN) alpha plus ribavirin (RBV) in the retreatment of chronic hepatitis C (CHC) in patients who previously failed combination standard IFN plus RBV or IFN monotherapy has not been well established. **METHODS:** Three hundred and twenty-one CHC patients including virologic nonresponders to combination IFN plus RBV (n = 219) or IFN monotherapy (n = 47), and relapsers to combination therapy (n = 55) were randomized to receive PEG IFN alpha-2b 1.5 microg/kg per wk plus RBV 800 mg per day (Regimen A, n = 160) or PEG IFN alpha-2b 1.0 microg/kg per wk plus RBV 1,000-1,200 mg per day (Regimen B, n = 161) for 48 wks. **RESULTS:** Sustained virologic response (SVR) occurred in 16% of the overall study population (Regimen A vs B, 18%vs 13%, p= 0.21), in 8% of the combination therapy nonresponders (10%vs 6%, p= 0.35), in 21% of the IFN monotherapy nonresponders (16%vs 27%, p= 0.35), and in 42% of the combination therapy relapsers (50%vs 32%, p= 0.18). In nonresponders to prior combination therapy, HCV ribonucleic acid levels <100,000 copies/mL at the end of the prior treatment course were associated with an increased SVR compared with levels \geq 100,000 copies/mL (21%vs 5%, p= 0.002). In the overall study population, genotype 1 patients had lower SVR rates than others (14%vs 33%, p= 0.01), and African Americans had lower SVR than Caucasians (4%vs 18%, p= 0.01). **CONCLUSION:** Combination therapy with PEG IFN alpha-2b plus RBV is more effective in patients who relapsed after combination standard IFN plus RBV than in nonresponders to either combination therapy or IFN monotherapy. There was no significant effect of dosing regimen.

Frequency of hepatitis C in pregnancy and pregnancy outcome. Jaffery T, Tariq N, Ayub R, Yawar A. J Coll Physicians Surg Pak. 2005 Nov;15(11):716-9.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16300710&query_hl=5

OBJECTIVE: To determine the frequency of HCV infections in pregnant women, to find out the risk factors for HCV infection in pregnant women and to compare pregnancy outcome of the sero-positive women with sero-negative women. **DESIGN:** Case-control study. **PLACE AND DURATION OF STUDY:** Shifa International Hospital, Islamabad, from June 2001 to May 2002. **Patients and Methods:** Study was conducted on 947 booked pregnant women who were screened for HCV antibodies during antenatal consultation and were admitted for delivery in labour room. At the time of admission in labour ward, medical records of all patients were reviewed for anti HCV antibody testing and the presence of risk factors for HCV infection. Previous vaginal deliveries with episiotomy, previous surgeries, blood transfusions, and D&C for abortion or dysfunctional uterine bleeding were taken as independent variables. The obstetric outcome variables studied were: completed weeks of gestation by mother, birth weight and apgar score of newborns. The risk factors under study and the outcome variables were compared among HCV positive and negative women through a case-control study and measures of association calculated. **RESULTS:** The proportion of HCV sero-positivity among pregnant woman in our study was 3.27%. Among all the risk factors under study, previous surgery was found to have a significant association with HCV positive status of women (p=0.001). Other variables did not have significant association with HCV positive status in our study. There was no statistical difference in the mean birth weight of newborns (p= 0.94), mean Apgar score of newborns (p= 0.73) and mean gestational period among HCV positive cases and controls (p= 0.47). **CONCLUSION:** Prevalence of hepatitis C in pregnant women was 3.27%. Past history of surgical procedures was the most important factor for transmission of hepatitis C virus infection. No adverse effect on pregnancy outcome was observed in terms of gestational age, Apgar score and baby weight when compared with the controls.

Response of hepatitis C genotype-4 naive patients to 24 weeks of Peg-interferon-alpha2b/ribavirin or induction-dose interferon-alpha2b/ribavirin/amantadine: a non-randomized controlled study. El-Zayadi AR, et al. Am J Gastroenterol. 2005 Nov;100(11):2447-52.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16279899&query_hl=5

BACKGROUND AND AIM: Currently, pegylated interferon is the most effective therapy for hepatitis C but its cost is out of reach of most patients in the developing countries. The aim of this study was to assess the response rate of genotype-4 patients to 24 wks of peg-interferon-alpha2b (Peg-IFN-alpha2b) and ribavirin (RBV) or interferon-alpha2b (IFN-alpha2b) with RBV and amantadine (AMD) as an alternative option. **METHODS:** In a controlled study, 180 biopsy-proven naive chronic hepatitis C patients were allocated into three groups based on their financial affordability to any of the study regimens. Group I (control) comprised 40 patients who received Peg-IFN-alpha2b in a flat dose of 100 mug/wk (the dose available in Egypt) plus RBV 1,000-1,200 mg per day based on body weight for 48 wks. Group II comprised 70 patients who received the same regimen for 24 wks. Group III comprised 70 patients who received induction-dose triple therapy (IDTT) in the form of IFN-alpha2b 3 MU once daily for the first 4 wks then reduced to TIW for 20 wks plus RBV 1,000-1,200 mg per day based on body weight and AMD 100 mg twice daily for 24 wks. Six patients from group I, eight patients from group II, and four from group III discontinued the study either due to financial limitations and/or intolerable adverse effects of the drugs. **RESULTS:** Intention-to-treat analysis revealed that sustained virological response (SVR) achieved in 22 (55.0%), 34 (48.6%), and 20 (28.6%) in groups I, II, and III, respectively. Adherence-to-treatment analysis (80/80/80) revealed that SVR achieved in 22 (64.7%), 34 (54.8%), and 20 (30.3%) in groups I, II, and III, respectively. In absence of eradication of hepatitis-C-virus-RNA at week 12, there was virtually no chance of achieving SVR. These data collectively may indicate that genotype 4 is "not difficult to treat" as previously reported. **CONCLUSION:** Response of genotype-4 patients to 24 wks of Peg-IFN-alpha2b/RBV did not significantly differ from 48 wks, but was significantly higher than IDTT. Although SVR achieved by IDTT is less than Peg-IFN-alpha, yet it might provide a second option when the latter is not affordable. Early virological response should be used as a predictor to SVR to avoid unnecessary expenses in nonresponders patients.

Influence of alcohol on the progression of hepatitis C virus infection: a meta-analysis. Hutchinson SJ, Bird SM, Goldberg DJ. Clin Gastroenterol Hepatol. 2005 Nov;3(11):1150-9.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16271348&query_hl=5

BACKGROUND & AIMS: A convincing, yet inconsistent, pattern has emerged that demonstrates increased progression of HCV-related liver disease with heavy alcohol use. The aim was to perform a meta-analysis to quantify the effect of alcohol on cirrhosis risk among persons infected with HCV. **METHODS:** A meta-analysis of 20 articles, involving more than 15,000 HCV chronically infected persons, published between 1995 and 2004 was undertaken to explore the relationship between advanced liver disease and the consumption of alcohol. **RESULTS:** The pooled relative risk of cirrhosis associated with heavy alcohol intake (defined in the range of at least 210-560 g per week) was 2.33 (95% confidence interval, 1.67-3.26) by the random effects model. The risk of HCV-related liver disease associated with heavy alcohol intake increased with severity of the outcome; the lowest (1.63; 95% confidence interval, 1.22-2.17) and highest (3.54; 2.14-5.85) pooled relative risk estimates were obtained for advanced fibrosis and decompensated cirrhosis, respectively. The regression effect of alcohol might, however, be underestimated in studies investigating the risk of HCV-related cirrhosis because they necessarily include patients undergoing liver biopsy and could therefore under-represent heavy alcohol users. **CONCLUSIONS:** The evidence overwhelmingly shows a worsened outcome for those with chronic HCV and concurrent alcohol use. Studies varied widely in their definition of significant alcohol intake, and so the true threshold above which alcohol accelerates HCV disease progression remains uncertain. Alcohol consumption should be minimized as much as possible in those who have chronic HCV until a safe threshold is more definitively determined.

Hepatic steatosis in chronic hepatitis C: impact on response to anti-viral treatment with peg-interferon and ribavirin. Guidi M, Muratori P, et al. Aliment Pharmacol Ther. 2005 Nov

15;22(10):943-9.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16268968&query_hl=5

BACKGROUND: There is increasing evidence that hepatic steatosis contributes to the progression of liver fibrosis, whereas its impact on the efficacy of anti-viral treatment is still under investigation. **AIM:** To evaluate the effect of steatosis on the outcome of combined anti-viral treatment. **METHODS:** We studied 102 consecutive naive patients with chronic hepatitis C receiving combined anti-viral therapy (peg-interferon alpha-2b and ribavirin). **RESULTS:** Fifty (49%) of 102 patients had evidence of hepatic steatosis (29 grade 1, 16 grade 2 and 5 grade 3). Sustained virological response was similar in patients with and without steatosis (58% vs. 56%); moreover, the grade of steatosis did not affect the rate of sustained virological response (grade 1: 58%, grade 2: 56% and grade 3: 60%). Patients with steatosis had significantly higher serum levels of aspartate transaminase, alanine transaminase and gamma-glutamyltransferase ($P = 0.007$, 0.004 and 0.03 , respectively), higher histological activity ($P = 0.03$), more advanced stage of fibrosis ($P = 0.0394$) and more often hepatitis C virus genotype 3 ($P = 0.04$).

CONCLUSIONS: Our findings suggest that hepatic steatosis in chronic hepatitis C, irrespective of its grade, is not a negative prognostic factor of response to combined anti-viral therapy, even when the histological and biochemical profile of the disease is more aggressive.

The Effect of Ribavirin on Bone Density in Patients with Chronic Hepatitis C Treated with Interferon-Ribavirin Therapy. Urganci N, et al. *J Pediatr Gastroenterol Nutr.* 2005 Nov;41(5):650-652. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16254525&query_hl=5

OBJECTIVE: The objective of this study was to investigate the effects of ribavirin on bone mineral metabolism in patients with chronic hepatitis C who had been treated with interferon and ribavirin. **METHODS:** Twenty patients (3 female, 17 male) with chronic hepatitis C were enrolled. Age range was 6 to 15 years (mean \pm SD, 11.15 ± 2.3 years). Thirteen patients received combined interferon alpha-2b and ribavirin therapy (Group 1), and 7 patients received only interferon alpha-2b (Group 2). Both groups were treated for 12 months. Bone mineral density, z-scores and biochemical bone markers were evaluated in both groups before and after treatment. **RESULTS:** There were no significant differences between the groups in age or gender. Mean lumbar vertebral bone mineral density and mean z-scores in groups 1 and 2 before and after treatment were not significantly different. In both groups, serum and urinary biochemical values and bone markers were all normal and there were no differences between the pretreatment and post-treatment values. **CONCLUSION:** Contrary to studies in adults, we did not find any ribavirin-dependent changes related to bone mineral metabolism in our pediatric study groups. Further studies are needed to obtain more detailed information about the effects of ribavirin on bone mineral density.

Psychological implications of hepatitis C virus diagnosis. Gill ML, Atiq M, Sattar S, Khokhar N. *J Gastroenterol Hepatol.* 2005 Nov;20(11):1741-4.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16246195&query_hl=6

BACKGROUND AND AIMS: Hepatitis C virus (HCV) diagnosis causes significant psychological stress and anxiety. We thought it would be important to illustrate the anxiety caused by HCV diagnosis in patients from the developing world. **METHODS:** This study was conducted at the Shifa International Hospital, Islamabad, between February 2004 and April 2004. All patients who were recently diagnosed with HCV (those who tested positive to anti-HCV and HCV polymerase chain reaction) were given a questionnaire that compared stress due to HCV infection with four other variables, including death of a close family member, divorce, loss of source of income and move to another city. We also analyzed the anxiety level among these patients using the Beck Anxiety Inventory (BAI). **RESULTS:** We studied 98 patients and 100 healthy controls. Thirty-one (31.63%) patients who were diagnosed with HCV presented only with fatigue. Sixty-three (64.28%) patients admitted that diagnosis of HCV interfered with their daily life in some way. Among the newly diagnosed cases, 48 (48.97%) patients had moderate to severe

anxiety (BAI Class B and C). Multi-logistic regression analysis showed that anxiety was related to HCV-related stress ($P < 0.002$) and self-perceived severity of disease ($P < 0.001$). HCV diagnosis was significantly more stressful than divorce (59.87 vs 70.95; $P < 0.013$), loss of source of income (50.52 vs 70.80; $P < 0.001$), and a move to another city (28.32 vs 70.80; $P < 0.001$). **CONCLUSIONS:** Diagnosis with HCV is reported to be more stressful than divorce, loss of source of income and a move to another city.

Safe use of pegylated interferon/ribavirin in hepatitis C virus cirrhotic patients with hypersplenism after partial splenic embolization.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16215426&query_hl=6

BACKGROUND AND AIMS: Partial splenic embolization (PSE) is a non-surgical alternative for the treatment of hypersplenism. Thrombocytopenia precludes the use of pegylated interferon (peg-IFN) and ribavirin in cirrhotic patients with hepatitis C virus (HCV). We aimed to evaluate the role of PSE as a procedure allowing combined HCV therapy in this setting. **METHODS:** A retrospective analysis of the safety and rate of sustained virological response (SVR) after a full-dose course of peg-IFN plus ribavirin in eight HCV cirrhotic patients with severe hypersplenism undergoing PSE at a tertiary centre in Madrid, Spain, from May 2002 to August 2004. **RESULTS:** Six patients (75%) were in Child-Pugh class B (median score 7). PSE significantly improved the mean platelet ($P = 0.012$), leucocyte ($P = 0.017$) and haemoglobin ($P = 0.035$) levels, and prothrombin activity ($P = 0.012$). After a mean of 20 weeks after PSE all patients started weight-adjusted ribavirin plus peg-IFN-alpha2b ($n = 6$) or 180 microg/week of peg-IFN-alpha2a ($n = 2$). Six subjects (75%) completed therapy with no peg-IFN dose reductions; the dose of ribavirin was reduced in two patients reaching haemoglobin levels of less than 10 g/dl (one also received erythropoietin and granulocyte colony-stimulating factor because of neutrophil counts < 300 cells/microl). Three patients (38%) achieved SVR. Portal vein thrombosis was observed in 50% of patients, but did not preclude antiviral therapy. The pathogenic mechanism was multifactorial. It was successfully managed with anticoagulant therapy in two cases. **CONCLUSIONS:** PSE allowed the safe use of peg-IFN plus ribavirin in HCV cirrhotic patients with severe cytopenias who otherwise would never have been treated. The rate of SVR was 38%.

A long-term follow-up and management study of hepatocellular carcinoma patients surviving for 10 years or longer after curative hepatectomy. Shimada K, Sano T, Sakamoto Y, Kosuge T. Cancer. 2005 Nov 1;104(9):1939-47.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16177997&query_hl=6

BACKGROUND: The aims of the current study were to elucidate the clinicopathologic characteristics and disease recurrence patterns of patients with hepatocellular carcinoma (HCC) who survived for 10 years or longer after undergoing an initial hepatectomy. **METHODS:** Between January 1987 and December 1993, 578 patients underwent potentially curative hepatectomy at the study institution. Disease recurrence and follow-up data were available for 481 of these patients, who then were followed for more than 10 years after the initial hepatectomy. Fourteen clinicopathologic features were compared between the 10-year survivors and those patients who died within 10 years after the surgery. The risk factors for disease recurrence, the recurrence status, time to recurrence, and treatment modalities for recurrence were examined among the 10-year survivors. **RESULTS:** There were 105 10-year survivors (21.8%), including 42 disease-free survivors (8.7%). Favorable independent factors found to be correlated with 10-year survival were age < 55 years, a plasma retention rate of indocyanine green at 15 minutes of $< 15\%$, the presence of a solitary tumor, the absence of intrahepatic metastases, the absence of portal vein invasion, and the absence of underlying cirrhosis. A negative test for the hepatitis C antibody and the absence of intrahepatic metastases were found to be independent predictive factors for 10-year disease-free survival among the 10-year survivors. **CONCLUSIONS:** The results suggest that younger patients without underlying cirrhosis who have a solitary HCC that does not demonstrate vascular invasion might survive

for longer than 10 years after the initial hepatectomy. In addition to close surveillance in such patients after hepatectomy, repeat hepatectomy, local ablation therapy, and transhepatic arterial chemoembolization may contribute to long-term survival, even if disease recurrence occurs.

Depression and anxiety in patients with hepatitis C: prevalence, detection rates and risk factors.

Golden J, O'dwyer AM, Conroy RM. Gen Hosp Psychiatry. 2005 Nov-Dec;27(6):431-8.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16271658&query_hl=5

OBJECTIVE: We examined a group of patients awaiting interferon treatment for hepatitis C to estimate the prevalence and detection rates of and risk factors for mood disorders. **METHODS:** The Structured Clinical Interview for DSM-IV Axis I Disorders: Clinician Version was used to detect psychiatric disorder. Self-completion instruments were used to rate symptom severity, subjective cognitive function, work and social adjustment, stigma, acceptance of illness and treatment satisfaction. **RESULTS:** The 90 participants included 23 women (26%); 33 (37%) had contracted hepatitis C iatrogenically, 42 (47%) through injecting drug use and the remainder (17%) were of unknown origin. There was a 28% 1-month prevalence of depressive disorders, 72% of whom were previously undiagnosed, and a 24% prevalence of anxiety disorders, 86% previously undiagnosed. Current methadone maintenance was strongly associated with risk of depression (odds ratio, 5.0; 95% CI, 1.08-23.0). After adjustment for age and sex, depression was associated with poorer work and social adjustment, lower acceptance of illness, higher illness stigma, poorer reported thinking and concentration, and higher levels of subjective physical symptoms (all $P < .05$). Anxiety disorders were uncorrelated with any risk factor. **CONCLUSIONS:** Depression and anxiety have high prevalences in hepatitis C, and are largely undetected and treated. Depression, but not anxiety, is associated with adverse experiences of illness.

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Relationship between early HCV kinetics and T-cell reactivity in chronic hepatitis C genotype 1 during peginterferon and ribavirin therapy.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16139918&query_hl=6

BACKGROUND/AIMS: To gain understanding of inter-individual differences of treatment response in hepatitis C virus genotype 1 (HCV-G1) patients, we investigated simultaneously the early HCV kinetics and virus-specific T-cell reactivity. **METHODS:** Thirty, treatment-naive HCV-G1 patients received peginterferon-alfa2a 180 microg/week plus ribavirin 1000-1200 mg/day, with blood samples collected prospectively at protocol time-points. HCV RNA was quantitated with a TaqMan assay with mathematical modelling of HCV decay. Virus-specific CD4+/CD8+ T-cells were enumerated by Elispot assays. **RESULTS:** HCV kinetic analysis identified two subgroups: fast (18/30) and slow (12/30) treatment-responders. Although these subgroups did not differ in any baseline characteristics, fast responders (FR) showed greater antiviral efficacy (epsilon) than slow responders (SR) (84.5 ± 3.2 vs. $65.2 \pm 7.0\%$, $P = 0.002$), and a higher rate of infected cell loss (delta) (0.56 ± 0.2 vs. 0.04 ± 0.02 , $P = 0.038$). The viral load drop (baseline to treatment week 4) was higher in FR vs. SR group (3.5 ± 1.1 vs. 1.4 ± 0.6 log₁₀IU/mL, $P < 0.001$). T-cell reactivity to HCV increased only in FR (after the loss of viraemia), but not in SR patients. **CONCLUSIONS:** Assessment of early viral and T-cell kinetics during treatment reveals marked differences amongst HCV-G1 patients and may provide a basis for treatment individualization. Enhancement of antiviral T-cell reactivity requires rapid viraemia clearance, rather than immunostimulation alone.

Hepatitis C virus-NS3P in relation to p53, p21,mdm2, p21-ras and c-erbB2 in hepatocarcinogenesis.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16246194&query_hl=6

BACKGROUND: The non-structural protein 3 (NS3P) of hepatitis C virus (HCV) genome was linked to the neoplastic transformation of normal hepatocytes in chronically infected patients. However, the exact mechanisms involved in this process are unidentified yet, especially in the Egyptian population where the commonest type is genotype 4. **METHODS:** We investigated 32 HCV reverse transcriptase-polymerase chain reaction (RT-PCR) positive hepatocellular carcinoma (HCC) cases and 18 morphologically normal hepatic tissues distant to tumors (MNT) for the correlation between HCV-NS3P, p53, p21(waf), mdm2, p21ras and c-erbB2 and DNA content by immunohistochemistry and image analysis. **RESULTS:** The NS3P expression was lower in HCC (65.6%) than in MNT (94.4%) patients. The expression level of studied genes in HCC was: p53 (56.25%), p21(waf) (43.7%), mdm2 (59.4%), p21-ras (73.3%) and c-erbB2 (75%). Whereas in MNT, it was 22.2, 61.1, 44.4, 41.2 and 77.8%, respectively. The NS3P expression showed a significant correlation with the presence of cirrhosis, chronic active hepatitis (CAH) and tumor grade ($P < 0.05$). c-erbB2 overexpression and p21(waf) loss were higher in MNT than in HCC patients, however, this did not reach a statistically significant level. There was a statistically significant correlation between NS3P, c-erbB2 and p21(waf) ($P < 0.01$). There was also a significant correlation between p21(waf) loss and CAH ($P = 0.01$) as well as between mdm2, c-erbB2 and cirrhosis ($P = 0.025$ and 0.001) in HCC cases. There was a statistically significant difference in the ploidy status between HCC and MNT, but there was no significant relationship between the ploidy status and other clinicopathological features. **CONCLUSION:** The carcinogenic effect of NS3P is probably exerted at an early stage of HCC possibly through a pathway involving c-erbB2 and p21(waf) alterations. In contrast, p53, p21ras and mdm2 alterations are late events in hepatocarcinogenesis and are usually associated with an aggressive phenotype.

The apolipoprotein [epsilon] 3 allele is associated with persistent hepatitis C virus infection.

Price DA, et al. Gut. 2005 Nov 18; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16299033&query_hl=5

BACKGROUND: Host genetic factors may significantly influence the ability to clear hepatitis C virus (HCV) following infection. HCV are associated with very-low-density lipoproteins (VLDL) and low-density-lipoproteins (LDL) in the host's circulation. Apolipoprotein E (APO-E) is found in VLDL and binds to potential receptors involved in HCV entry into cells, the LDL receptor and the scavenger receptor protein, SR-B1. The APO-E gene is polymorphic with three alleles coding for 3 isoforms: Apo-epsilon2, Apo-epsilon3 and Apo-epsilon4. The aim of this study was to assess if these functional polymorphisms determine disease outcome in HCV infected individuals. **METHODS:** The APOE genotype was determined in 420 Northern European patients with evidence of exposure to HCV. Genotype and allele distribution were compared with those of 288 healthy controls and progression of liver disease and viral clearance were analysed according to APOE allele status. **RESULTS:** The APOE*E2 and APOE*E4 alleles were both associated with a reduced likelihood of chronic infection (OR = 0.39, CI 0.211 - 0.728, $p = 0.003$ and OR = 0.6, CI 0.38 - 0.96, $p = 0.032$) and there was a notable absence of the E2E2 genotype in the HCV antibody positive group compared with the control population ($p = 0.0067$). Overall the genotypes carrying the E2 allele (E2,E3 and E2,E4) were associated with the equivalent of a 3 - 5 fold reduction in risk of chronic HCV infection (GRR = 0.36 and 0.20; respectively). **CONCLUSION:** This study indicates that functional APOE gene polymorphisms may be a determinant of outcome in HCV infection. We hypothesise that the E2 allele may protect against viral persistence via defective binding of HCV lipo-viral particles to the cellular receptors involved in entry of these infectious particles.

The modeled structure of the RNA dependent RNA polymerase of GBV-C Virus suggests a role for motif E in Flaviviridae RNA polymerases. Ferron F, BMC Bioinformatics. 2005 Oct 14;6(1):255 [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16225688&query_hl=3

BACKGROUND: The Flaviviridae virus family includes major human and animal pathogens. The RNA dependent RNA polymerase (RdRp) plays a central role in the replication process, and is thus a validated target for antiviral drugs. Despite the increasing structural and enzymatic characterization of viral RdRps, detailed replication mechanisms remain unclear at the molecular level. The hepatitis C virus (HCV) is a major human pathogen difficult to study in cultured cells. The bovine viral diarrhea virus (BVDV) is often used as a surrogate model to screen antiviral drugs against HCV. The structure of BVDV RdRp was recently published. It presents several differences relative to HCV RdRp. These differences raise questions about the relevance of BVDV as a surrogate.

Morphine Withdrawal Enhances Hepatitis C Virus Replicon Expression. Wang CQ, et al. Am J Pathol. 2005 Nov;167(5):1333-1340.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16251417&query_hl=1

We previously demonstrated that morphine enhances hepatitis C virus (HCV) replication in human hepatic cells. Here we describe the impact of morphine withdrawal (MW), a recurrent event during the course of opioid abuse, on HCV replicon expression in human hepatic cells. MW enhanced both viral RNA and protein expression in HCV replicon cells. Blocking opioid receptors by treatment with naloxone after morphine cessation (precipitated withdrawal, PW) induced greater HCV replicon expression than MW. Investigation of the mechanism responsible for MW- or PW-mediated HCV enhancement showed that both MW and PW inhibited the expression of endogenous interferon-alpha (IFN-alpha) in the hepatic cells. This down-regulation of intracellular IFN-alpha expression was due to the negative impact of MW or PW on IFN-alpha promoter activation and on the expression of IFN regulatory factor 7 (IRF-7), a strong transactivator of the IFN-alpha promoter. In addition, both MW and PW inhibited the anti-HCV ability of recombinant IFN-alpha in the hepatic cells. These in vitro observations support the concept that opioid abuse favors HCV persistence in hepatic cells by suppressing IFN-alpha-mediated intracellular innate immunity and contributes to the development of chronic HCV infection.

Protection against Chronic Hepatitis C Virus Infection after Rechallenge with Homologous, but Not Heterologous, Genotypes in a Chimpanzee Model. Prince AM, Brotman B, et al. J Infect Dis. 2005 Nov 15;192(10):1701-9. Epub 2005 Oct 6..

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16235167&query_hl=6

An open question for hepatitis C virus (HCV) vaccine development is whether the various genotypes of this virus protect against the development of chronic infection after heterologous infection with different genotypes. We approached this question by challenging chimpanzees that had recovered from HCV genotype 1a or 1b infection with 6 heterologous genotypes as well as with a homologous genotype (for chimpanzees originally infected with genotype 1a). All 9 chimpanzees rechallenged with a homologous genotype developed self-limited infections. Of 11 chimpanzees challenged with 100 chimpanzee infectious doses of heterologous genotypes, 6 developed self-limited infections, with peak viral loads in acute-phase serum that were ~5-fold lower than those seen during primary infections. One chimpanzee (which had recovered from genotype 1b infection and was rechallenged with genotype 6a) did not develop viremia but did show an anamnestic cell-mediated immune response after rechallenge. Four of the 11 chimpanzees rechallenged with heterologous genotypes developed chronic infections with the genotypes used for rechallenge. These findings suggest that a universally protective HCV vaccine may need to incorporate epitopes from multiple genotypes.

HIV/HCV COINFECTION

Increased Hepatocyte Fas Expression and Apoptosis in HIV and Hepatitis C Virus Coinfection.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=1

[6206071&query hl=6](#)

BACKGROUND: Chronic hepatitis C disease (CHC) follows an accelerated course in human immunodeficiency virus (HIV) coinfection. The reasons for this are unclear. Fas-mediated hepatocyte apoptosis is involved in the pathogenesis of hepatitis C virus (HCV) infection. We sought to compare the expression of Fas on hepatocytes and irreversible apoptosis of hepatocytes among patients with CHC with and without HCV/HIV coinfection. **METHODS:** Fas-immunostained hepatocytes were semiquantified, and apoptotic hepatocytes were detected by staining caspase-cleaved cytokeratin 18 filaments and counted across the entire section of liver-biopsy specimens from HCV-infected patients with and without HCV/HIV coinfection. **RESULTS:** One hundred thirty-four HCV/HIV-coinfected and 100 HCV-infected patients were included. HCV/HIV coinfection was associated with both diffuse distribution of Fas-stained hepatocytes (adjusted odds ratio [AOR], 7.4 [95% confidence interval {CI}, 3.8-14.4]) and with apoptotic hepatocyte counts greater than the median (AOR, 2.5 [95% CI, 1.5-4.5]). In HCV/HIV-coinfected patients, CD4(+) cell nadir <200 cells/mL was associated with both Fas expression (AOR, 2.9 [95% CI, 1.3-6.8]) and hepatocyte apoptosis (AOR, 2.3 [95% CI, 1.1-4.9]). **CONCLUSION:** HCV/HIV-coinfected patients show higher levels of hepatocytes expressing Fas and undergoing irreversible apoptosis than do HCV-infected patients. However, low CD4(+) cell nadirs in coinfecting patients are associated with hepatocyte Fas expression and apoptosis.

Presence of Hepatitis C Virus (HCV) RNA in the Genital Tracts of HCV/HIV-1-Coinfected Women.

Nowicki MJ, J Infect Dis. 2005 Nov 1;192(9):1557-65. Epub 2005 Sep 29.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16206070&query hl=6

BACKGROUND: Hepatitis C virus (HCV)-infected women--in particular, those coinfecting with human immunodeficiency virus type 1 (HIV-1)--can transmit infection to their children and sex partners. **METHODS:** The present study was conducted to analyze the presence of HCV RNA in cervicovaginal lavage (CVL) fluid from 71 women (58 HCV/HIV-1-coinfecting women and 13 HCV-infected, HIV-1-uninfected women) enrolled in the Women's Interagency HIV. **STUDY RESULTS:** HCV RNA was detected (by a commercial polymerase chain reaction assay) in CVL fluid from 18 (29%) of the HIV-1-infected women and from none of the HIV-1-uninfected women (P<.05). Multivariate analysis revealed that risk factors for the presence of HCV RNA in CVL fluid were HCV viremia (odds ratio [OR], 16.81; P=.02) and HIV-1 RNA in CVL fluid (OR, 19.87; P=.02). This observation suggests local interactions between HIV-1 and HCV in the genital tract compartment. There was no correlation between HCV RNA in CVL fluid and CD4, CD8, or CD3 cell counts, HIV-1 RNA viremia, the number of leukocytes in CVL fluid, or HIV-1 therapy. Furthermore, in 3 of 5 analyzed patients who had a detectable CVL HCV RNA load, we found viral variants differing in the 5' untranslated region that were present neither in plasma nor in peripheral-blood mononuclear cells. **CONCLUSIONS:** Our observations point to the importance of the genital tract compartment, in which local HCV replication could be facilitated by local HIV-1 replication.

Hepatitis C virus in the semen of men coinfecting with HIV-1: prevalence and origin.

Briat A, Dulioust E, et al. AIDS. 2005 Nov 4;19(16):1827-35.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16227790&query hl=6

OBJECTIVE: To compare the prevalence of hepatitis C (HCV) RNA in semen from men infected with HCV and those coinfecting with HIV-1/HCV and to study the origin of HCV shed in semen. **DESIGN:** Two prospective studies (HC EP09 and BINECO) included 120 HCV-positive men, 82 coinfecting with HIV-1; all had positive HCV RNA detection in blood. **METHODS:** Paired blood and semen samples were collected for HCV RNA detection and quantification in seminal plasma and in blood serum; repeated semen samples were obtained for 45 men. HCV RNA was sought in spermatozoa and non-sperm cells. Phylogenetic analysis of the HVR-1 region of HCV compared the quasispecies in blood serum and seminal plasma of two men. **RESULTS:** HCV RNA was more frequently found in the semen of men

coinfecting with HIV-1 (37.8%) than in those with only HCV infection (18.4%) ($P = 0.033$). HCV RNA detection in semen was intermittent and was positive in at least one semen sample of 42.8% of HIV-1/HCV-coinfecting men who provided repeated samples. Men with HCV-positive semen had significantly higher HCV load in blood than men with HCV-negative semen ($P = 0.038$). Phylogenetic comparison of HCV quasispecies in blood and in semen showed no evidence of HCV replication in genital leukocytes; however, a phenetic structure was observed between compartments ($P < 0.001$). **CONCLUSIONS:** HCV particles in semen originate from passive passage from blood, with preferential transfer of some variants. Nearly half of HIV-1/HCV-coinfecting men may intermittently harbour HCV in their semen. Recommendations of protected sex for HIV-infected individuals should be reinforced.

Validation of a simple model for predicting liver fibrosis in HIV/hepatitis C virus-coinfecting patients. Al-Mohri H, Cooper C, Murphy T, Klein MB. HIV Med. 2005 Nov;6(6):375-8

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16268817&query_hl=5

OBJECTIVES: Recently, several models incorporating laboratory measurements have been validated for use as surrogate markers for liver fibrosis in hepatitis C virus (HCV) mono-infection, the simplest of these being the aspartate aminotransferase (AST) to platelet ratio index (APRI). We evaluated how well the APRI predicts significant hepatic fibrosis in patients with HIV/HCV coinfection. **METHODS:** Forty-six HIV/HCV-coinfecting patients who underwent liver biopsy and had concomitant laboratory measurements (± 3 months) were included in the study. Significant fibrosis was defined as F2-F4 using Batt and Ludwig scoring ($= 3$ Ishak). $APRI = [(AST/upper\ limit\ of\ normal)/platelet\ count\ (10^9/L)] \times 100$. We used sas proc logistic (SAS Institute, Cary, NC) to calculate the area under the receiver operating curve (ROC) (AUC). Sensitivities, specificities, positive predictive value (PPV) and negative predictive value (NPV) were compared using cut-offs previously identified in the literature. **RESULTS:** Thirty-three of 46 patients (72%) had significant fibrosis on biopsy. For significant fibrosis, the area under the ROC for the APRI was 0.847 ± 0.057 . APRI scores > 1.5 (the higher cut-off) were 100% specific and 52% sensitive; PPV was 100% and NPV 45%. Scores < 0.5 (the lower cut-off) were 82% sensitive and 46% specific in ruling out significant fibrosis (PPV 79%; NPV 50%). **CONCLUSIONS:** A simple model incorporating readily available laboratory data is highly predictive of significant fibrosis in HIV/HCV coinfection and could serve as a biopsy-sparing measure, thus making treatment more accessible for this population.

Serological markers of autoimmunity in patients infected with hepatitis C virus: impact of HIV co-infection. Adeyemi OM, et al. HIV Med. 2005 Nov;6(6):371-4.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16268816&query_hl=5

OBJECTIVES: We sought to evaluate the prevalence, predictors and significance of autoantibody expression in patients with chronic hepatitis C (CHC) with or without HIV co-infection. **METHODS:** Retrospective review of laboratory and histologic data for all patients with CHC who had a liver biopsy available. HIV status was documented in all patients. Results analyzed in SPSS10, Chicago, IL, a p value < 0.05 was considered significant. **RESULTS:** 170 patients with hepatitis C viremia, including 107 (63%) HIV co-infection, who had testing for anti-nuclear antibody (ANA) or anti-smooth muscle antibody (ASMA) and anti-mitochondrial antibody (AMA) were included in the study. Overall, 63% (74/117) of patients were ASMA seropositive and 6% (9/153) were positive for ANA. All 117 patients tested for AMA were negative. HIV co-infected patients were significantly more likely to be ASMA positive 71% (53/75) compared to those with hepatitis C alone (50%) [$P = 0.026$]. There were no significant differences in age, gender, race, risk group, alanine aminotransferase (ALT) levels or grade of inflammation on histology between autoantibody positive and negative patients. ASMA positive patients had significantly higher globulin levels ($P = 0.036$) and a trend towards more bridging fibrosis or cirrhosis. Patients with autoantibody expression rarely had histologic features of AIH. **CONCLUSION:** We found a high rate of ASMA seropositivity in our cohort of patients with chronic hepatitis C, and HIV co-infection was associated with significantly higher rates of ASMA expression. Autoantibody expression was not

associated with demographic or clinical characteristics and does not necessarily preclude antiviral therapy.

Histological Findings and Clinical Characteristics Associated with Hepatic Steatosis in Patients Coinfected with HIV and Hepatitis C Virus. Marks KM, et al. *J Infect Dis.* 2005 Dec 1;192(11):1943-9. Epub 2005 Nov 2.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16267765&query_hl=5

BACKGROUND: Hepatic steatosis, a common histological finding in hepatitis C virus (HCV)-infected patients, is associated with severity of fibrosis. The prevalence and significance of steatosis in patients coinfecting with human immunodeficiency virus (HIV) and HCV are not well characterized.

METHODS: To determine the prevalence and severity of steatosis, a single pathologist evaluated liver-biopsy samples from 106 patients coinfecting with HIV and HCV but without hepatitis B infection (negative results for hepatitis B surface antigen) for findings associated with steatosis or steatohepatitis and viral hepatitis. Medical records were reviewed retrospectively to elucidate risk factors for steatosis.

RESULTS: Steatosis was present in 56% of biopsy samples, with moderate to severe grades in 9%. Severity of steatosis was associated with fibrosis (odds ratio [OR], 1.84 [95% confidence interval {CI}, 1.06-3.20]; $P=.03$) but not with necroinflammation. In multivariate analysis, the severity of steatosis was associated with lower levels of high-density lipoprotein cholesterol (OR, 0.71 per 10-mg/dL increase [95% CI, 0.52-0.95]; $P=.02$), higher body-mass index (OR, 1.30 per kg/m² increase [95% CI, 1.13-1.49]; $P<.001$), and the presence of lipodystrophy (OR, 3.82 [95% CI, 1.13-12.88]; $P=.03$). There was a trend toward an association between the severity of steatosis and fibrosis in multivariate analysis (OR, 1.69 [95% CI, 0.91-3.16]; $P=.10$). **CONCLUSIONS:** In patients coinfecting with HIV and HCV, hepatic steatosis is common and associated with more-advanced fibrosis. Lower levels of high-density lipoprotein cholesterol, higher body-mass index, and lipodystrophy are potentially modifiable risk factors associated with the severity of steatosis.

Differences in HCV-specific T cell responses between chronic HCV infection and HIV/HCV co-infection. Dutoit V, et al. *Eur J Immunol.* 2005 Nov 22; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16304636&query_hl=5

Hepatitis C virus (HCV)-specific CD4(+) and CD8(+) T cell responses were investigated using a panel of 728 overlapping peptides spanning the whole HCV genome in 47 HCV mono-infected and 26 HIV/HCV co-infected individuals using the IFN-gamma ELISPOT assay and flow cytometry. The frequency of HCV-specific T cell responses was similar (approximately 40%) in both groups, but the breadth of the T cell responses tended to be reduced in HIV/HCV co-infected individuals. Of interest, 23 new HCV-derived epitopes were identified, and CD4(+) HCV-specific T cell responses were detected overall in a proportion similar to CD8(+) T cell responses. A tendency towards a dominant CD8(+) T cell response was associated with HIV/HCV co-infection. HCV-specific CD8(+) T cells secreted both IL-2 and IFN-gamma, although a reduction in the percentage of IL-2/IFN-gamma-secreting cells was observed in HIV/HCV co-infected individuals. The increase in CD4(+) T cell counts after antiretroviral therapy in HIV/HCV co-infected individuals was not associated with restoration of HCV-specific T cell responses. Altogether, these results provide new insights into the characterization of HCV-specific T cell responses in HCV mono-infected and HIV/HCV co-infected individuals.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Silymarin treatment of viral hepatitis: a systematic review. Mayer KE, Myers RP, Lee SS. *J Viral Hepat.* 2005 Nov;12(6):559-67.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=1

[6255756&query hl=81](#)

Silymarin from the milk thistle herb (*Silybum marianum*) is used by many patients with chronic viral hepatitis, but its efficacy remains unknown. We performed a systematic review of silymarin for the treatment of chronic viral hepatitis B and C. An exhaustive search strategy identified 148 papers that studied silymarin compounds in liver disease. Of these, four trials included patients with hepatitis C, one included hepatitis B patients, and two, unspecified chronic viral hepatitis. However, only one trial exclusively studied patients with hepatitis C, and none involved patients with only hepatitis B. Silymarin treatment resulted in a decrease in serum transaminases compared with baseline in four studies, and compared with placebo in only one study. There is no evidence that silymarin affects viral load or improves liver histology in hepatitis B or C. No studies were found that investigated the use of silymarin concomitantly with interferon, nucleoside analogues, or other conventional treatments for hepatitis B or C. **In conclusion**, silymarin compounds likely decrease serum transaminases in patients with chronic viral hepatitis, but do not appear to affect viral load or liver histology. Nevertheless it may be worthwhile to determine its effects in conjunction with standard antiviral treatment.

MISCELLANEOUS

Infection of tupaia hepatocytes with hepatitis C virus in vitro. [Article in Chinese]

Zhao XP, Zhonghua Gan Zang Bing Za Zhi. 2005 Nov 20;13(11):805-807.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16313720&query hl=5

OBJECTIVE: *Tupaia belangeri* (tree shrew) has a close phylogenetic relationship with primates and has been shown to be susceptible to a variety of human viruses. This study was conducted to investigate whether or not hepatitis C virus (HCV) could infect primary tupaia hepatocytes (PTHs) in vitro.

METHODS: Serum-derived HCV was cultivated with PTHs, and then positive and negative strand HCV RNA in PTHs, as well as the encapsidated HCV RNA in the culture medium were detected to evaluate the infection. Virus from the culture medium of the infected PTHs was passed to naive PTHs, and the quasispecies of HCV were compared among the inoculum and PTHs after infection and passage.

RESULTS: Both positive and negative strand HCV RNA were detected in PTHs after infection. The negative strand RNA was detectable from day 5 to day 10 after infection, while the positive strand RNA was positive up to day 14. HCV RNA, which was RNase resistant, could be detected from the culture medium of the infected PTHs from day 3 to day 14. Production of infectious virions of PTH were demonstrated by passage HCV to naive PTHs. Compared analysis of HCV quasispecies after infection and passage showed that PTHs were selectively infected with defined HCV quasispecies, and new quasispecies emerged in PTHs after passage. **CONCLUSION:** The present study strongly indicates that PTHs could be infected by HCV and support HCV replication in vitro. Our results would be helpful for the establishment of a tupaia model of HCV infection.

The prevalence of HCV antibody in South Australian prisoners. Miller ER, Bi P, Ryan P. J Infect. 2005 Nov 25; [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16313963&query hl=5

OBJECTIVES: The study was aimed at identifying the hepatitis C virus (HCV)-antibody status of prisoners incarcerated in South Australia in order to develop an HCV prevalence estimate for the whole prison system. **METHODS:** The health records of persons incarcerated within eight prisons (accommodating approximately 93% of the jurisdiction's adult incarcerated population) were audited for evidence of HCV infection, age, sex, Indigenous status (Australian Aboriginal or Torres Strait Islander) and date of entry to prison. These data were analysed using both univariate and multivariate techniques.

RESULTS: Among 1347 prisoners (1254 males and 93 females), 30.2% were HCV-antibody positive. After excluding those with no history of testing, HCV-antibody prevalence rose to 41.3% (males 39.8%, females 66.1%). HCV-antibody positivity was significantly associated with age, sex and Indigenous status

in both univariate and multivariate analyses. **CONCLUSIONS:** Consistent with the literature, the prevalence of HCV infection in the SA prison system appears to be extremely high. This study suggests that HCV prevention efforts in prison settings should be considered as an important priority.

Pathways of care and resource utilization in a national cohort of patients with transfusion-acquired hepatitis C. Brant L et al. , J Viral Hepat. 2005 Nov;12(6):618-26.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16255763&query_hl=5

The Hepatitis C Strategy and Action Plan for England recommend that all individuals testing positive for hepatitis C virus (HCV) should be referred to a specialist centre for assessment and care. One key aim is to reduce the number of people progressing to liver disease and therefore reduce the associated costs. The aims of this paper are to describe the care pathways and evaluate resource utilization in a cohort of 826 patients with transfusion-acquired hepatitis C enrolled in the HCV national register. We reviewed data extracted from patient notes to establish pathways of care since HCV-positive diagnosis through to May 2002, and to document all treatment, liver biopsy and hospital usage for each patient. Type of care was classified into specialist-interest in HCV-related care, other-hospital care or general practitioner (GP)-led care. Over 70% of patients were referred to specialist care following HCV diagnosis. Patients who were older or who had normal liver function were less likely to be referred to specialist-care. Between first diagnosis and May 2002, no patients were referred from GP to specialist-care. Less than half of this cohort had undergone liver biopsy and only 18% had been treated. Younger patients and those with abnormal liver function were more likely to have undergone liver biopsy and to have received treatment. Analysis of care histories of patients with transfusion-acquired hepatitis C suggest that changes are needed in the care and management of patients with HCV infection, if the recommendations of the HCV strategy and action plan are to be fully implemented.