

# Digestive Disease Conference: Day Two

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## Abstract 213

### Clinical Significance of Pegylated Interferon Induced Neutropenia: Results from the WIN-R Trial

*Furqaan Ahmed, Ira M. Jacobson, Robert S. Brown Jr., Nezam Afdhal, Raymond Rubin, James Spivey, Bradley Freilich, Fredric Regenstein, David Bernstein, Robert Doig, Clifford Brass, Win-R. Study Group*

#### Background:

Neutropenia occurs commonly in patients treated with pegylated interferon and ribavirin (*Manns, Lancet* 2001;358:958-65). The clinical significance of this neutropenia remains uncertain.

#### Aim:

The aim of this study was to determine if there is a correlation between the occurrence of neutropenia and the development of serious infections while on combination therapy.

#### Method:

We provide data on infectious serious adverse events (SAE) from the WIN-R Trial, a U.S. multicenter study comparing fixed (800mg) versus weight based (800-1400mg) daily dosing of ribavirin in combination with pegylated interferon alfa-2b (pegintron) 1.5 µg/kg/week. We reviewed serious infections and ANC data at weeks 0,2,4,8,12,18,24,30,36,42, and 48.

#### Results:

Of the 4243 patients enrolled in the study, 30 (0.7%) developed infectious serious adverse events (SAE) while on therapy. These 16 male and 14 female patients ranged in age from 35-63 years (mean 47 years). The infections included pneumonia (10), UTI (3), cellulitis (3), URTI (2), abscess (4), and one case each of cat scratch disease, salmonella colitis, furuncle, meningitis, appendicitis with perforation, tibial hardware infection, bacteremia, and invasive *C. jejuni* diarrhea.

Reviewing available data, 24 patients received antibiotics, 27 were hospitalized, and 7 required surgical intervention. One patient died with pneumonia. Complete ANC data was available for 25 of the infectious SAE patients. The ANC fell below 1000 at some point in 14 (56%) patients. The overall mean nadir ANC in all patients was 1317±822. The mean nadir ANC for the SAE patients was not significantly different than that for the rest of the patients (1198±757 vs. 1318±823, p=0.46).

The proportion of patients who developed ANC <750 was similar in both groups (20%). In patients with infectious SAEs, the mean ANC prior to infection was significantly higher than the mean nadir ANC (2286±1676 vs. 1198±757, p=0.005). The nadir and pre-infection ANCs were the same in only 15% (3/20) of patients. The mean timing of the nadir ANC and the onset of infection were similar (week 18 vs. week 16). Additional data regarding this issue is being accumulated.

#### Conclusions:

- (1) Patients who develop serious infections while on combination therapy with pegylated interferon alfa-2b and ribavirin do not have significantly lower mean nadir ANCs.

- (2) Infectious serious adverse events generally did not occur at the time of nadir ANC.
- (3) Criteria and utility for dose reduction of peginterferon and the use of granulocyte stimulating factor to treat neutropenia require further assessment.

## Abstract 215

### The Safety, Efficacy and Pharmacokinetics of Peginterferon alfa-2a (40KD) (PEGASYS®) in Children With Chronic Hepatitis C

*Kathleen B. Schwarz, Johns Hopkins University School of Medicine, Parvathi Mohan, Children's National Medical Center, Michael Narkewicz, University of Colorado School of Medicine, Department of Pediatrics, Jean Pappas Molleston, James Whitcomb Riley Hospital for Children, Helen S. Te, University of Chicago, Sylvia Hu, Susan Sheridan, Matthew Lamb, Stephen C. Pappas, George Harb, Roche, Nutley*

#### Introduction:

The prevalence of children infected with HCV in the United States is estimated at 0.2% in children aged under 12 years and 0.4% in those aged 12 to 19 years. New infections are primarily acquired by perinatal (vertical – mother to child) transmission. Generally, children infected with HCV exhibit no symptoms, have normal or near normal ALT levels and their rate of disease progression is slower compared to adults with infected with HCV. Currently, no therapies are FDA approved for treatment of chronic hepatitis C in children.

#### Objective:

The objective of this study was to investigate the safety, efficacy and pharmacokinetic characteristics of peginterferon alfa-2a (40KD) PEGASYS® and study the HCV kinetics in children aged 2 to 8 years with chronic hepatitis C infection.

#### Study Design:

- ◆ PEGASYS® SC once weekly for 48 weeks
- ◆ Dose: Body Surface Area (BSA) in m<sup>2</sup> X 180 µg/1.73 m<sup>2</sup>
- ◆ Blood sampling:
  - Pre-dose at wk 1, 4, 8, 12, 24, 40 and 48
  - Post-dose (wk 1 and 24) at 24, 96 and 168 hr
- ◆ Serum concentrations analyzed by a quantitative ELISA
- ◆ Bayesian estimates of pharmacokinetic parameters

#### Patients/Methods (Number of Patients = 14):

<b>Male, Female - number</b>	<b>8,6</b>
Mean age (range)	4.4 yrs (2-8)
Mean weight (range)	20.1 Kg (13.3-45.3)
Mean height (range)	106.9 cm (86-131)
Mean ALT ± SD	73.5 IU ± 28.7
Mean AST ± SD	66.9 IU ± 20.3
HCV genotype (1, non-1)	13, 1
HCV RNA (= 850000); >850000 IU/mL)	10, 4
Mode of transmission:	
Parinatal, transfusion, unknown	11, 1, 2
Histology (noncirrhotic/cirrhotic)	14/0

## Results:

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### Characteristics of Children with Sustained Virological Responses

Male, Female	5,1
HCV genotype (1, non-1)	6,0
HCV RNA (= 850000; > 850000 IU/mL)	5,1
Baseline ALT (= 3 x ULN)	6

### Adverse Events – probably related to treatment

pyrexia	11
headache	6
fatigue	3
vomiting	3
nausea	2
injection site reactions	2
irritability	2

### Premature Withdrawal

- ◆ Five patients withdrew after completing 24 to 47 weeks of treatment.

### Reasons for withdrawal include:

- ◆ Adverse events/intercurrent illness (elevated transaminases [2], elevated triglycerides [1])
- ◆ Administrative error (last dose not taken)
- ◆ Refusal to continue with treatment

### Sustained Virological Response Rate

Six children obtained a sustained virological response rate (SVR) (HCV RNA-negative at week 72) with a total sustained virological response rate 42.9%.

## Conclusions:

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The authors concluded that Pegasys monotherapy based on body weight was safe, effective and well tolerated in children. In addition, the sustained virological rate of 42.9% for children age 2 to 8 was similar to that found in adults. These results support further studies of Pegasys with and without ribavirin in children with chronic hepatitis C.

## Abstract 216

### Aggressive Psychiatric Intervention Based on Clinical Suspicion, Not Standardized Depression Scores, Increases Adherence to Pegylated Interferon and Ribavirin Therapy for Hepatitis C

Jennifer Moss, Anshu Chandra, Paul Gaglio, Silvia Hafliger, Lorna Dove, Steve Lobritto, Ira Jacobson, Robert Brown

## Introduction/Conclusions:

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Neuropsychiatric side effects of pegylated interferon often limit therapy for HCV. Depression is the most common reason for treatment discontinuation. Early treatment of depression may increase the efficacy of interferon-based therapy.

## Aim:

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The aim of this study was to investigate the utility of standard depression scores (Beck Depression Index

(BDI) and Center for Epidemiologic Studies-Depression (CES-D) for predicting depression and of early psychiatric intervention on adherence to pegylated interferon and ribavirin therapy.

### ***Methods:***

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55 treatment naive HCV patients at one site were entered into WINR-R, a study comparing standard ribavirin 800mg qd to weight based ribavirin, 800-1400mg qd, both with PEG-Intron 1.5 ug/kg q week.

We report on 39 patients with complete follow-up. BDI and CES-D surveys were completed at weeks 0, 4, 12, 24, 48 and 24 weeks post-therapy; investigators were blinded to results. Psychiatric evaluation was performed by 1 psychiatrist if there was current (+ad, n=6) or prior (+hx, n=8) depression, or if they reported depression on routine questioning.

Data on psychotropic medication and outcomes was collected.

### ***Results:***

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30 of 39 patients completed surveys. During therapy, 40 (20% at entry), 30, and 6% used antidepressants, sleeping medications, and benzodiazepines respectively. 30% used no psychotropic medications. There were no dose reductions for psychiatric side effects. The 2 surveys were analyzed individually, and were normalized to produce 1 data set.

Patients requiring antidepressants had mean maximum scores of 19 (BDI), 27 (CES-D), and 12 (normalized) compared to 10, 13, and 6 respectively for those not requiring antidepressants(p<0.05). BDI and CES-D scores increased at week 4, were higher at week 48, and remained elevated 6 months after therapy.

### ***Conclusions:***

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Aggressive psychiatric intervention led to a 0% need for discontinuation of therapy for psychiatric side effects. Clinical assessment achieved this high adherence rate, as individual BDI and CES-D scores were too variable to predict the need for antidepressants. 6 months after end of therapy, patients did not resume their baseline psychiatric profile.

## **Abstract 217**

### **Histological Improvement in Patients with Pegylated Interferon Alpha-2b plus Ribavirin Who Were Previously Non-Responders to Rebetron**

*Khaled Selim, Christopher Hyun, Jonathan Jensen, Stephen J. Rossi, Kip Lyche, Larry Weprin, Deanna Oliver, Wendy Y. Myers, Beth Ziegler, Cynthia Behling, Tarek Hassanein*

### ***Introduction:***

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Approximately 60% of patients who were treated with Rebetron therapy were non-responders to treatment. Re-treatment of this population targets viral eradication and/or improvement in histology.

### ***Aim:***

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The aim of our study is to determine the impact of 48 weeks of therapy with Pegylated interferon Alpha-2b plus Ribavirin on Histological Activity Index (HAI) and Fibrosis.

### ***Methods:***

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193 patients who were virologically non-responders to standard combination are the subjects of this study. The mean age of the patients was  $48.4 \pm 7.3$  years. 127 males and 66 females were enrolled in the study. 160 patients were genotype 1, 8 patients were genotype 2, and 3 patients were genotype 3.

Patients were randomized to either Peg-IFN alpha 2b 1.5 mcg/kg QW + Ribavirin 800 mg QD or Peg-IFN alpha 2b 1.0 mcg/kg QW + Ribavirin 1000-1200 mg QD for 48 weeks.

A single pathologist scored the pre and post biopsies using the modified Knodell scoring system.

### Results:

49 patients with paired liver biopsies finished 48 weeks of treatment at the time of this analysis. 17 (35%) were PCR negative and 32 (65%) were PCR positive. The overall HAI improved after treatment from  $5.91 \pm 2.26$  to  $4.47 \pm 2.36$  ( $p = 0.000$ ), while fibrosis score improved from  $2.65 \pm 1.09$  to  $2.22 \pm 1.37$  ( $p = 0.006$ ). This histologic improvement was significant in patients who achieved HCV-RNA negative PCR by the end of treatment. (table)

### Conclusion:

Significant histologic improvement was only seen in patients who achieved viral clearance by week 48. Patients that were PCR positive at week 48 achieved significant improvement in hepatic inflammation but not in fibrosis. Combination of Peg-Intron and Ribavirin is very effective in improving histologic activity in patients who failed to clear HCV RNA.

	<i>PCR Negative @ Week 48</i>		<i>PCR Positive @ Week 48</i>	
	Pre-Treatment	Post-Treatment	Pre-Treatment	Post-Treatment
<i>HAI</i>	$5.29 \pm 2.1$	$3.35 \pm 1.9$	$6.25 \pm 2.3$	$4.97 \pm 2.4$
<i>p value</i>	0.0008		0.019	
<i>Fibrosis</i>	$2.65 \pm 1.2$	$2.12 \pm 1.36$	$2.66 \pm 1.1$	$2.28 \pm 1.4$
<i>p value</i>	0.029		0.064	

## **Abstract 230**

### **HCV Vertical Transmission: Long-Term Prospective Study**

*Simone Ferrero, Pietro Lungaro, Bianca Marisa Bruzzone, Cristina Gotta, Giorgio Bentivoglio*

### Objective:

The purpose of this study is to determine the rate of vertical transmission of hepatitis C virus (HCV) in at-risk neonates and to assess the effect of possible risk factors. This study also aims to evaluate the possible adverse effects of HCV infection on pregnancy.

### Methods:

From March 1990 to March 2000, 182 women were found to be anti-HCV positive (using ELISA and RIBA) when tested during pregnancy. 17 women delivered twice during the study period. There was 1 twin pregnancy. 12 mother-infant pairs who attended our department during the same period were excluded from the study because the children were lost at follow-up.

In the aggregate, 170 mothers and 188 babies were included in this study. All women were analyzed for HCV-RNA by polymerase chain reaction (PCR). The babies were followed-up until HCV-antibody clearance or until the diagnosis of HCV-infection. For each HCV-positive mother a control group of five seronegative women ( $n = 850$ ) was matched for age, BMI, parity and number of foetuses.

## ***Results:***

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- ◆ The vertical transmission rate was 2.7% overall, and it was higher in HIV co-infected women (5.4%, 2/37) than in HIV negative (2.0%, 3/151).
- ◆ All HCV-infected infants were born to mothers who had HCV viremia at delivery.
- ◆ Mothers who transmitted infection had higher levels of viremia (mean 5.92 mEq/ml  $\times 10^6$ , 95% CI 4.10 to 7.43) than mothers who did not transmit HCV infection (mean 1.35 mEq/ml  $\times 10^6$ , 95% CI 0.33 to 1.50), the difference was statistically significant ( $p = 0.010$ , t-Student test).
- ◆ The proportion of caesarean section, premature delivery and obstetric complications was similar in HCV infected-women and in control group ( $p < 0.001$ )
- ◆ birth weights were similar for the two groups.

## ***Conclusions:***

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- ◆ The risk of HCV vertical transmission is very low in HCV-positive/HIV-negative women and it is restricted to infants born to women with positive HCV-RNA.
- ◆ High maternal viral load is predictive of the vertical transmission.
- ◆ We have found no evidence of an adverse effect of HCV infection on pregnancy.

## **Abstract 232**

### **Steatosis Influences the Early Virologic Response Rate in Patients with Chronic Hepatitis C Infection**

*Heather M. Patton, Keyur Patel, Marc Vallee, Cynthia Behling, David Bylund, Paul J. Pockros, John G. McHutchison*

## ***Background:***

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Early virological response (EVR) is defined as a fall in HCV RNA levels by  $\geq 2 \log_{10}$  units at 12 weeks of treatment. Failure to achieve EVR is highly predictive of eventual non-response, and may be used to design early stopping rules for chronic hepatitis C genotype-1 infected patients. Steatosis is believed to lower SVR rates in chronic hepatitis C patients.

## ***Aim:***

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To assess whether the degree of steatosis prior to initiation of therapy has a negative impact on EVR rates.

## ***Methods:***

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Patients that received initial therapy for HCV with interferon (or peginterferon) and ribavirin at a single center were included in the study. Pre-treatment liver biopsy specimens were blindly evaluated for steatosis by recording a percentage of affected hepatocytes and thereafter assigning a categorical grade [grade 0 (0-2%), grade 1 (3-29%), grade 2 (30-59%), grade 3 ( $\geq 60\%$ )]. Baseline demographic information and fasting laboratory values were determined at the time of liver biopsy. HCV RNA levels were measured at baseline and week 12 of therapy. Covariate effects were assessed using stepwise logistic regression analysis with EVR as the outcome.

## ***Results:***

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One hundred sixty patients were included in the analysis of which 115/160 (72%) achieved an EVR.

Genotype-1 (GT-1) patients that achieved EVR appeared more likely to have grade 0 steatosis than grades 1-3, compared to those that did not have an EVR (71% v. 42%;  $p=0.003$ ). Similar differences were not observed in GT non-1 patients. Age, GT-1 and fat percentage were selected as significant predictors of EVR in a stepwise analysis (see table).

When controlling for effects such as fibrosis stage, gender, genotype and BMI, GT-1 ( $p=0.007$ ) and fat percent ( $p=0.046$ ) remained significant predictors of EVR. Parameter estimates indicated that an increase in fat of 1% was associated with a 4.7% decline in predicted odds of an EVR (for fat percentages from 0 to 25%). As expected, HCV GT non-1 patients had a 7 fold greater EVR rate compared to GT-1 patients.

### ***Conclusions:***

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Increased steatosis is an independent variable that may reduce the likelihood of achieving EVR with combination therapy in chronic hepatitis C patients. Future prospective studies assessing EVR should also consider steatosis as an important factor that may influence treatment outcome.

<i>Variable</i>	<i>Parameter Estimate</i>	<i>p-value</i>	<i>Log odds Estimate</i>
<i>Age</i>	-0.157	0.047	0.945
<i>Fat Percentage</i>	-0.048	0.027	0.953
<i>Genotype - 1</i>	-1.995	0.0001	0.1.36

### ***Editor's Notes:***

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- ◆ The author commented that the data from this study speaks well for lifestyle modifications that include weight loss to increase treatment response rates and should be studied more closely studied in larger trials.

## **Abstract 233**

### **Interferon and Interferon plus Ribavirin in Hepatocellular Carcinoma Prevention: A Prospective Study on Patients with HCV Related Cirrhosis.**

*Francesco Azzaroli, Giuseppe Mazzella, Esterita Accogli, Silvia Giovanelli, Davide Trere', Costanza Mazzeo, Giovanni Nigro, Anna Miracolo, Francesca Lodato, Antonio Colecchia, Constance Mwangemi, Davide Festi, Massimo Derenzini, Enrico Roda*

### ***Introduction:***

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Hepatocellular carcinoma is the most common cancer worldwide. There is enough data now to suggest that interferon prevents hepatocellular carcinoma (HCC) development in patients with HCV-related cirrhosis but what if any effect does ribavirin have? The effect of interferon is modest and seems more pronounced among sustained responders. Data on the preventive effect of more powerful therapeutic schemes on HCC development are lacking.

### ***Patients/Methods:***

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A total of 101 patients (62 males and 39 females, mean age 55.1 +/- 1.4) with histologically proven (biopsy) HCV related liver cirrhosis and compatible biochemistry and ultrasonography were enrolled in the study. Ultrasonography was performed every 6 months. Liver biopsy was performed on all focal lesions detected by ultrasound. Follow-up after treatment lasted an average of 6 years. To evaluate hepatocyte proliferation, Ag-NOR proteins were measured in hepatocyte nuclei present in 50 consecutive microscopic fields using a specific computer-assisted imaging system. The percentage of hepatocytes with an AgNOR area >7 square

micrometers (indicative of a proliferative state) was expressed as AgNOR-PI (AgNOR-Proliferative Index) (cut-off=25).

41 patients (27 males, 14 females) were only followed up after the end of an yearly treatment with IFN-alpha2b (6 MU/day for 30 days followed by 3 MU/day for 11 months) (Old Treatment Control Group = OTCG).

60 naives patients (35 males, 25 females) were stratified according to sex and AgNOR-PI and then randomized in two groups: 30 patients were treated with IFN-alpha2b (6MU/day for a month then 3 MU/day for 11 months) +Ribavirin (1 g/day for 11 months) (Treatment Group = TG) and the remaining served as controls (Control Group = CG).

Non responders or relapsers in the TG received further IFN/ribavirin treatments after 6 mo withdrawal. Initial patient characteristics were similar in both groups.

### Results:

The AgNOR-PI was significantly lowered by IFN; 9 patients (26%) out of 35 with basal AgNOR-PI higher than 25 developed HCC, while 2 (3%) out of 66 with basal AgNOR-PI lower than 25 developed tumors ( $p<0.001$ ).

Two patients of OTCG (both non responders) developed HCC during 6 yrs of follow-up after about 50 months from IFN withdrawal. None of the 30 patients in the TG developed HCC, while 9 (30%) patients in the CG developed HCC during follow-up. The Kaplan-Mayer survival curves showed statistically significant differences among OTCG vs CG ( $p<0.004$ ) and TG vs CG ( $p<0.003$ ). The HCC annual rate of incidence in the CG was 5%.

### Conclusion:

In conclusion IFN/ribavirin treatment associated with re-treatment courses of non responder patients seems to produce the best results in terms of HCC prevention. AgNOR-PI is an useful marker of possible HCC development.

### Editor's Notes:

- ◆ Treatment (either IFN alone or in combination with RBV) should be considered in persons with cirrhosis because they are at a high risk for developing HCC
- ◆ It appears that retreatment has some benefit in preventing HCC in the non-responder
- ◆ Proliferative Index (PI) was significantly lower in patients treated ( $p<0.001$ ). The incidence of HCC in the high PI subset was 26% versus 3% in the subset of patients with a low PI. Gg-NOR – PI is a useful marker
- ◆ There was a recommendation not to use alcohol during the trial
- ◆ This is an intent to treat trial – every patient that started the trial was counted in the final results. 11 HCC tumors (9 in the control group and 2 in non-responders  $p=0.001$ )

## **Abstract 234**

### **Use of Carotenoid-Based Functional Food Minimizes the Severity of Ribavirin-Induced Anemia in Patients with Chronic Hepatitis C: a Randomized Study**

*Filomena Morisco, Antonella Carbone, Vincenzo Fogliano, Riccardo Marmo, Alberto Ritieni, Antonio Ascione, Giuseppina De Luise, Alfonso G. Lanza, Nicola Caporaso*

## ***Background:***

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Oxidative stress plays a major role in the physiopathology of hemolytic anemia during ribavirin therapy. The efficacy of antioxidant supplementation (vitamin C and E as pure compounds) is still controversial. Reduction or withdrawal from ribavirin therapy in three large trials showed a range of 8-9%

## ***Aim:***

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We conducted a study to verify if the supplementation with an antioxidant-rich tomato-based functional food (FF) reduces the anemia during peginterferon (PEG-IFN) and ribavirin (RBV) therapy for chronic hepatitis C (CHC).

## ***Patients/Methods:***

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A functional food with high content of natural antioxidants and demonstrated high carotenoid bioavailability was developed. 100g of tomato-based functional food contains the following nutritional and antioxidant compounds: Nutrition per 100g is kcal=162, fats 10g, carbohydrate 10g, protein 8g. Antioxidant compounds per 100g are vitamin E (mg) 1.6, total flavonoids (mg) 5.3 (quercetin 4.3mg and narngenin 1.0mg), total carotenoids (mg) 23.

We enrolled 92 patients (70M/22F) with CHC treated with pegylated interferon alpha 2b 1.5µg/kg plus 1000-1200mg RBV combination therapy for 6 months. 46 of them received a daily dose (100g.) of functional food (FF) – group 1, and 46 did not receive the functional food - group 2. At baseline, the groups were similar for demographics (M/F, body weight, age); mean hemoglobin (Hb) levels (15.09 vs. 14.9 g/dl, p= ns), and both group received similar mean dose of RBV(13.51, +/- 1.09 vs. 13.39 +/- 1.52 mg/kg, p=ns).The effect of antioxidant activity was assessed comparing the compliance to the start dose of RBV and the Hb levels during the first three months of treatment.

## ***Results:***

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There was no difference in withdrawal rates between group 1 and group 2 (no patients in either group had a Hb fall below 8.5g/dl) however only 4/46 (8.7%) patients in group1 had to reduce daily RBV dose, while RBV reduction was necessary for 14/46 (30.4%) in group 2 (p= 0.09). Dose reductions of RBV occurred when the Hb fell to between 8.5 and 10g/dl.

## ***Conclusions:***

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Results demonstrated that our FF limit the severity of ribavirin-related anemia and improve the tolerance to the initial dose of ribavirin in patients with chronic hepatitis C.

## ***Editor's Notes:***

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- ◆ The authors concluded that a regular intake of carotenoid-based functional foods improved ribavirin tolerance and decreased severity of antiviral induced anemia
- ◆ Men in the study arm taking FF tended to tolerate the diet better than females
- ◆ Control did not abstain from antioxidant consumption however the author did point out that it takes 0.8kg to make 100g of functional food (the daily amount) and therefore it is very unlikely that the control was taking anything even close to the diet
- ◆ The limitations of this study include the lack of testing of the bioavailability of ribavirin

## **Abstract 235**

# Reasons for Discontinuation of Treatment for Chronic Hepatitis C. An Interim Analysis of the Frontier Trial.

Matthew Nichols, Lisa Forman, Marcelo Kugelmas

## Introduction:

Treatment with Pegylated interferon and ribavirin may be an option for patients with chronic hepatitis C who have failed Rebetron combination therapy (Reb) and/or interferon monotherapy (IFN). Sustained virological results are generally higher in a clinical setting because there is usually a person that is dedicated to providing support and care. However in 'real world' practice there is not that level of support and care to obtain the highest possible response rates in patients by completing their full course of therapy. It is known that adherence is closely related to SVR as reported by McHutchinson 2002 Gastroenterology.

In this report of patients treated with pegylated interferon alpha 2b and RBV, the intent to treat overall SVR for genotype was 42% with an SVR >50% for those patients that were compliant to therapy versus a 34% SVR for those patients that were not compliant to therapy.

## Methods:

Two hundred twelve patients with chronic hepatitis C who have failed Rebetron and/or IFN were randomized to treatment with Peg-Intron and ribavirin (P+R) for 24, 36, or 48 weeks. Patients were enrolled and treated at one of six academic institutions or one of twelve community practices. All received Peg-Intron 1.5 mcg/kg/weekly and ribavirin 800 mg/d. This is an interim report of the first 146 patients treated. Reason for discontinuation of treatment was assessed for each patient who did not complete his or her assigned therapy.

## Results:

Of the 146 patients, 60 were treated at academic institutions and 86 were treated at community practices. Eighty-eight of the 146 patients completed the full course of treatment to which they were randomized: 45 of 60 at academic institutions (75%) and 43 of 86 at community practices (50%;  $p$  vs. academic institutions = 0.002).

Of the 58 patients that did not complete the full course of treatment, 40 patients chose to drop out of the study: 9 of 60 at academic institutions (15%) and 31 of 86 at community practices (36%;  $p$  vs. academic institutions = 0.005). Twelve patients in community practices and 4 in academic institutions dropped out of the study within the first twelve weeks ( $p = 0.18$ ).

The most common reasons cited for dropping out were related to the usual flu-like and neuro-psychiatric side effects of therapy in 13 cases (4 in academic institutions vs. 9 in community practices;  $p = 0.55$ ), not recorded (9, all in community practices), and non-compliance with the protocol (1 in academic institutions vs. 5 in community practices). Regarding non-compliance; there was one case in the academic institution and 5 cases in the community practices. Eighteen serious adverse events led to treatment termination (6 in academic institutions and 12 in community practices) and included complaints of chest pain (3), suicidal ideation (2), severe depression (2), and irritability/aggressiveness (2). No significant effect of age, gender, BMI, or race was seen on adherence rates.

## Discussion:

Adherence with therapy during the first 12 weeks of Pegylated interferon and ribavirin therapy and then throughout the remainder of the treatment course has been associated with successful treatment outcome. This data shows a disparity between academic and community institutions regarding the rates of patient-initiated discontinuation of treatment (i.e. dropouts), and suggests that treatment response rates and rates of

compliance typically reported in the literature may not accurately depict rates of success that can realistically be expected.

#### **Editor's Notes :**

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- ◆ The investigators did not control for mild depression
- ◆ Exclusion criteria for alcohol was 40 grams for males; 20 grams for women
- ◆ There were no differences in drop outs due to funding from the academic versus community settings
- ◆ All centers had prior experience with treating HCV. The experience level at all sites was prior management of >100 HCV patients
- ◆ Study coordinator at all sites although the study coordinator was not necessarily a mid-level practitioner (NP, PA)
- ◆ There were no dominant centers driving the academic and community disparities

### **Abstract 237**

#### **Micro-nutrients and Liver Injury in the U.S. Population**

*Constance E. Ruhl, James E. Everhart*

#### **Background & Aims:**

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Oxidative stress is thought to play a role in the liver injury due to nonalcoholic steatohepatitis (NASH). Hepatic iron may promote liver injury, whereas certain vitamins and minerals (antioxidants) may inhibit it, but few clinical studies have examined such relationships. We analysed the associations of serum iron measures and antioxidant concentrations with abnormal serum alanine aminotransferase (ALT) activity in a national, population-based study.

#### **Methods:**

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Serum transferrin saturation and serum iron, vitamins C and E, selenium, and five carotenoid concentrations were measured in 13,605 adult participants in the third U.S. National Health and Nutrition Examination Survey, 1988-1994.

Exclusions included excessive alcohol consumption, hepatitis B or C, and iron overload. Liver injury was indicated by elevated serum ALT activity (> 43 U/L). Serum nutrient concentrations were expressed as deciles (10th percentiles). All analyses incorporated sample weights and the design effects of the survey.

#### **Results:**

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- ◆ Elevated ALT activity was found in 3.1% of the population.
- ◆ In univariate analysis, factors associated with abnormal ALT activity ( $p < 0.05$ ) included higher serum transferrin saturation and iron and selenium concentrations, and lower serum vitamin C, alpha carotene, beta carotene, and lutein/zeaxanthin concentrations.
- ◆ In multivariate logistic regression analyses, elevated ALT was positively associated with increasing deciles of transferrin saturation and iron concentration and negatively associated with increasing deciles of alpha carotene, beta carotene, beta cryptoxanthin, and lutein/zeaxanthin concentrations (table 1).
- ◆ A variable combining the five carotenoid measures was also negatively associated with abnormal ALT (odds ratio per decile increase = 0.89, 95% CI=0.83-0.95). Vitamin C was inversely associated, but only at the highest serum concentrations.

<b>Serum nutrient (deciles)</b>	<b>OR</b>	<b>95% CI</b>
<i>Transferrin saturation</i>	1.10	1.03-1.18
<i>Iron</i>	1.13	1.06-1.21
<i>Vitamin C</i>	0.96	0.90-1.02
<i>Vitamin E</i>	1.04	0.96-1.13
<i>Selenium</i>	1.05	0.99-1.12
<i>Alpha carotene</i>	0.82	0.72-0.94
<i>Beta carotene</i>	0.91	0.86-0.96
<i>Beta cryptoxanthin</i>	0.91	0.84-0.99
<i>Lutein/zeaxanthin</i>	0.90	0.84-0.96
<i>Lycopene</i>	0.95	0.89-1.02

**Conclusion:**

In this large, national, population-based study, the risk of liver injury most likely due to NASH was associated with increased serum iron and decreased serum antioxidants, particularly carotenoids.

**Abstract 249**

**The Impact of Protease Inhibitors (PI) on the Histologic Spectrum of Liver Disease in HCV-HIV Coinfection.**

*Richard K. Sterling, Mary S. Wilson, Arun J. Sanyal, Velimir A. Luketic, R. T. Stravitz, Melissa J. Contos, A. S. Mills, Mitchell L. Shiffman*

**Introduction:**

HCV-HIV coinfection is common. With the initiation of HAART, patients with HIV are now living longer. Most studies on liver histology in coinfection were performed prior to HAART and its impact on liver histology is not clear. Although the use of PIs have been suggested to reduce progression of fibrosis, this remains controversial.

**Aim:**

To assess the impact of Protease Inhibitors on the spectrum of liver disease in HCV-HIV coinfection.

**Methods:**

A retrospective analysis of consecutive HCV-HIV coinfecting patients between 1998 and 2002 was performed. All patients were HIV +, HCV RNA +, and HBV surface antigen negative. A cohort of HIV uninfected HCV patients evaluated during the same time period were used as controls. Patients were excluded if they had recent or active opportunistic infection, creatinine > 1.5, platelet < 80,000, history of liver decompensation, or evidence of other liver disease. The Knodell histologic activity index (HAI) was assessed blindly regarding HAART therapy and advanced fibrosis was defined as bridging fibrosis or cirrhosis. Data are expressed as mean (+ SD).

**Results:**

The demographics of 101 coinfecting patients, mean age 43, 75% male and 82% African American, reflect our urban HIV clinic population. The mean HIV load was 1.52 log copies/ml and 48% had undetectable HIV RNA. The mean CD4 count was 528 cells/mm<sup>3</sup> (range 52-2332) and 11% had CD4 < 200. Data on HAART use was available in 93 patients of which 92% were on a mean of 3.02 (range 0-7) antiretroviral medications

including nucleoside reverse transcription inhibitors (NRTIs) (98%), non-NRTIs (45%), and PIs (54%). When patients were stratified by use of PI, we observed no significant differences in virologic, immunologic, biochemical, or histologic parameters between those whose HAART regimen included a PI compared to those who did not or to HIV uninfected controls.

### Conclusions:

Despite a high frequency of normal ALT, HCV-HIV patients on stable HAART have a significant proportion with advanced fibrosis. The use of Protease Inhibitors had little impact on biochemical and histologic parameters of HCV. Prospective studies are needed to determine the impact of Protease Inhibitors on HCV disease progression. Until then, the use of a Protease Inhibitors in the treatment of HIV in HCV coinfecting patients should be dictated by the need to control HIV and not to decrease the severity of HCV related liver disease.

Group	N	CD4 cells/mm <sup>3</sup>	CD4<200 %	Log HIV RNA	ALT U/L	NL ALT %	HAI	Adv Fib %
HAART w/PI	47	468(254)	13	1.08 (1.66)	82 (54)	54	6.89 (3.7)	34
HAART w/o PI	46	590(420)	11	1.85 (1.90)	82 (51)	51	7.30 (3.5)	31
Controls	302	n/a	n/a	n/a	94 (70)	49	7.03 (3.0)	24

### Editor's Note:

Comments made during this session included:

- ◆ There was no difference between Protease Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors
- ◆ No differences were seen in ALT or HAI
- ◆ No differences were seen by race
- ◆ Steatosis – did not find much steatosis as compared to HCV mono infected

## **Abstract 250**

### **Viral Clearance Occurs Very Early During the Natural Resolution of Transfusion-acquired Hepatitis C Virus Infections**

*Elaine Eyster, Jeffrey Sanders, James Goedert*

#### Introduction:

It is generally accepted that about 20% of persons who acquire hepatitis C virus (HCV) infections recover and become HCV RNA negative, but the timing of viral clearance is poorly understood. We documented the timing of spontaneous HCV RNA clearance in 12 patients from a well-characterized hemophilia cohort. Hemophilia is an inherited disease that affects mostly males and prevents blood clotting. It is treated by lifelong injections of clotting factors made with serum obtained from multiple donors. There is almost a 100% incidence of HCV in hemophiliacs that received clotting factors contaminated with HCV before 1987.

#### Patients/Methods:

Ten were male and two were female. All were HIV negative and none had been treated with interferon. Duration of infection ranged from 15 to 24 years (median 19 years). HCV RNA assays were performed on

archived serum samples collected at most 2 months to 4 years after the primary HCV infection had occurred, using the COBAS Amplicor assay (Roche). PCR positive samples were quantitated with the Versant bDNA assay (Bayer) and genotyped with the InnoLiPA reverse hybridization assay (Bayer).

### Results:

HCV RNA was undetectable by PCR in the initial anti HCV positive samples from 8 patients (66%). In 3 patients, HCV RNA was detected by PCR but not by bDNA, and in one patient, it was detected at a low level by bDNA (4,839 IU/ml, cut off <615 IU/ml).

Eight of the 12 had been infected with HCV by age 8.5 years (range 2.5 to 54 years). By comparison, seven of 8 controls with persistent viremia matched for age, sex and duration of blood product exposure had results ranging from 4,644 to 678,515 IU/ml (median 43,532) ( $p=.0008$ ). PCR testing on samples collected longitudinally over the course of the next 10-20 years (median 6 per patient, range 3-10) revealed that three of the 4 patients with HCV RNA detectable in their initial samples cleared virus during the next year.

Three were genotype 1 and one was genotype 2. Overall, the maximum duration of infection before clearance:

- ◆ 7 months or less in 4 (36%) and
- ◆ 1-2 years in 6 patients (55%) with yearly samples.
- ◆ One patient had persistence of HCV RNA for 5 years before clearance while receiving only sterilized concentrates, demonstrating that clearance can occur once chronic infection is established.

Reinfection was observed in only one patient and occurred while he was receiving unsterilized clotting factor concentrates.

### Conclusion:

- ◆ We conclude that HCV clearance usually but not always occurs within 1-2 years after infection and is more likely in those with lower than in those with higher early viral loads.
- ◆ In the patients that spontaneously cleared HCV, ALT have remained normal and there has been no disease progression

## **Abstract 251**

### **HCV RNA Quasispecies Evolution Associated with End Stage Liver Disease in a Longitudinal Cohort of HCV and HCV/HIV Infected Hemophiliacs**

*Hong Qin, Susan D. Rouster, Erica Keenan, Paul S. Horn, Elaine Eyster, Margaret Koziel, James Goedert, Kenneth E. Sherman*

### Background:

Hemophilic patients who received blood products/factor concentrates prior to 1987 have among the highest rates of HCV infection often in association with HIV. We evaluated the HCV RNA quasispecies evolution in longitudinally collected specimens comparing those with progression to decompensated liver disease (ESLD) to those with compensated chronic hepatitis.

### Methods:

Serially collected serum samples were obtained from the NCI Multicenter Hemophilia Cohort Study (MHCS). Index cases were derived from patients who progressed to end stage liver disease. Controls were matched

for age, gender, duration of infection, presence or absence of HIV coinfection, and HCV genotype. Samples from early infection (E) were compared to those obtained after onset of ESLD in the index patient (L). The HVR1 coding region was amplified, subcloned and sequenced. Predicted amino acid sequences were compared for clonal variability and evolution. Complexity and diversity were determined.

### ***Results:***

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One hundred eleven subclones derived from 9 patients followed over a mean duration of 9.5 year (S.E.= 1.2 years) were sequenced and evaluated for non-synonymous amino acid substitution. At baseline, no statistically significant difference in quasispecies complexity was observed between outcome cohorts. However, subjects who clinically progressed to end stage liver disease demonstrated significantly decreased quasispecies complexity over time ( $p=0.016$ ) and compared to the control group in samples collected at the L timepoint ( $p=0.018$ ). In non-progressor patients, 75% of all species demonstrated variation of one or more amino acid. In contrast, only 37% of clones derived from patients who developed end stage liver disease demonstrated heterogeneity in their HCV envelope HVR1 amino acid sequence. Narrowing of the quasispecies distribution occurred in both HCV/HIV coinfecting and mono-infected patients who progressed to end stage liver disease. Nucleotide diversity also decreased in subjects developing ESLD. The mean Kimura pairwise difference comparison demonstrated the greatest evolution in HCV/HIV coinfecting patients who progressed to end stage liver disease.

### ***Conclusion:***

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Hemophiliacs with HCV coinfection appear to reduce their quasispecies complexity with one dominant species in subjects who progress to ESLD while non-progressor controls maintain their complexity by constant mutation. These data suggest that selection of fit mutants become the dominant species or decreased immune selection is associated with liver disease progression in hemophilic HCV infected patients.

## **Abstract 252**

### **Comparison of Hepatitis C Virus (HCV)-related Liver Disease Between Caucasians (C) and African Americans (AA): Analysis of HCV in the Virginia Department of Corrections (DOC).**

*Richard K. Sterling, Velimir A. Luketic, R. T. Stravitz, Arun J. Sanyal, Melissa J. Contos, A. S. Mills, Mitchell L. Shiffman*

### ***Introduction:***

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Differences in HCV between Caucasians and African Americans remain controversial. Previous studies have been limited by size and heterogeneity of the populations studied. Although HCV is common in the Department of Corrections, the spectrum of liver disease in this setting has not been well characterized and offers a unique opportunity to compare the spectrum of liver disease between Caucasians and African Americans in a relatively homogeneous population.

### ***Aim:***

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To describe the biochemical, virologic, and histologic spectrum of HCV in the Department of Corrections.

### ***Methods:***

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A retrospective analysis of consecutive inmates biopsied for chronic HCV between October 1998 and July 2002 was performed. All patients included were anti-HCV+, had a platelet count  $>70,000$ , an INR  $<1.4$ , and

no evidence of hepatic decompensation. Patients were excluded from analysis if they were HIV positive, HBV SAg positive, had evidence of other liver disease, or creatinine >2.0 mg/dl. HCV RNA and genotyping were obtained at time of biopsy and liver histology assessed by Knodell histologic activity index (HAI) with histologically significant disease defined as total HAI >4 or any degree of fibrosis and advanced disease as presence of bridging fibrosis (BF) or cirrhosis (Cx).

### ***Results:***

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Three hundred and two inmates meeting criteria were analyzed. The mean age was 41, 91% were male, and 51% Caucasian. The mean ALT was 94 U/l and 49% had a normal ALT at the time of biopsy. HCV RNA was positive in all tested and 80% were genotype 1. The total HAI was 7.03: 85% had significant hepatitis and 24% had advanced fibrosis. When stratified by race:

- ◆ African Americans were more likely genotype 1 (94% versus 67%;  $p < .001$ ) and have lower ALT (79 U/l versus 106 U/l;  $p = .01$ ) with similar overall HAI (6.99 versus 7.59;  $p = .09$ ) compared to Caucasians.
- ◆ While African Americans had slightly lower fibrosis scores (1.12 versus 1.40;  $p = .047$ ), there were no differences in percentage of advanced fibrosis (22 versus 28). Those with mild disease (HAI <5) had lower ALT values (68 U/l versus 98 U/l;  $p < .001$ ) and higher percent with normal ALT (70 versus 46;  $p = .004$ ) compared to those with significant disease.
- ◆ The sensitivity, specificity, positive and negative predictive values for a normal ALT to predict mild disease were 70%, 53%, 22% and 90% and for an elevated ALT to predict significant histology were 90%, 21%, 53%, and 69%, respectively.

### ***Conclusions:***

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Significant hepatitis is seen in the majority of inmates with HCV and 24% have advanced fibrosis. There were no clinically significant differences between Caucasians and African Americans. Because ALT had poor accuracy, liver biopsy is essential to identify those with significant or advanced histopathology that might benefit from anti-HCV therapy.

## **Abstract 1388**

### **Interaction of Steatosis and Non-Alcoholic Steatohepatitis (NASH) with Chronic Hepatitis C**

*Zobair M. Younossi, Arthur J. McCullough, Janus P. Ong, David S. Barnes, Anthony Post, Kevin D. Mullen, William Carey, Robert O'Shea, Gavin Levinthal, Terry Gramlich, Lisa M. Martin, Diane Bringman, Anthony S. Tavill, Roy Ferguson*

### ***Introduction:***

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Hepatic steatosis or superimposed NASH may affect HCV-related fibrosis and the efficacy of anti-viral therapy.

### ***Aim:***

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The aim of this study was to determine the relationship of hepatic steatosis and NASH with chronic hepatitis C (CH-C).

### ***Design:***

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Patients with CH-C and available liver biopsies who completed a regimen of pegylated interferon alpha-2b (PEG-IFN), ribavirin (RIBA) and amantadine (AMANT) were included {PEG-IFN 1.5 mcg/kg weekly, RIBA 1000-1200 mg/d and AMANT 200 mg/d for 4 weeks, followed by PEG-IFN 0.5 mcg/kg weekly, RIBA 1000-

1200 mg/d and AMANT 200 mg/d for another 20 weeks}.

Patients with undetectable HCV RNA at week 24 continued this regimen for 48 weeks and were followed for another 24 weeks. Patients with undetectable virus (<50 IU/mL) after 24 weeks of follow up were considered to have SVR. All biopsies were read by one hepatopathologist using METAVIR, modified HAI as well as a Fatty Liver Pathologic protocol.

Patients' baseline clinico-demographic data as well as virologic response were associated with the extent of steatosis (>33% vs. <33%) and the type of fatty liver (No Fatty Liver vs. Steatosis vs. NASH) seen on the biopsy.

### Results:

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Of 119 patients, 69% were male, age  $47.4 \pm 5.68$ , BMI  $29.0 \pm 4.99$ , waist/hip ratio (W/H)  $0.90 \pm 0.08$ , 79% being white, 84.2% with genotype 1, 6.7% with genotype 2, 7.5% with genotype 3, 0.8% with genotype 4, and 40% with advanced fibrosis (METAVIR F3 and 4). Patients with higher grade of steatosis (>33%, n=14) were more obese (BMI  $32.83 \pm 1.67$  vs.  $28.49 \pm 0.45$ ,  $p=0.034$ ), more likely to have HCV genotype 3 (21.4% vs. 5.7%,  $p=0.037$ ) and advanced fibrosis (64.3% vs. 37.1%,  $p=0.048$ ) than those patients with lower grade of steatosis (<33%, n=105).

Furthermore, in comparing patients with superimposed NASH (n=22) to those with Steatosis (n=49) and those without Steatosis (n=48), patients with NASH had more evidence of obesity (BMI:  $30.64 \pm 1.2$  vs.  $29.90 \pm 0.76$  vs.  $27.33 \pm 0.59$ ,  $p=0.008$ , W/H 0.97 vs. 0.91 vs. 0.87,  $p<0.001$ ) and advanced fibrosis (68.2% vs. 44.9% vs. 22.9%,  $p=0.001$ ).

Neither the extent of steatosis nor the presence of superimposed NASH had an impact on SVR. Race, gender and age did not affect extent of steatosis or presence of superimposed NASH.

### Conclusions:

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Markers of obesity (BMI and W/H) and HCV genotype 3 are associated with extent of steatosis and type of fatty liver. Higher grade of steatosis and superimposed NASH were associated with advanced fibrosis but not the efficacy of the anti-viral regimen.

## **Abstract 1603**

### **Combining INF alfa 2b with PEG-INF alfa-2b and Ribavirin in the treatment of Non-responders to previous therapy and Nieve Genotype 1 patients with Chronic Active Hepatitis C.**

*Scott M. Gioe*

### Introduction:

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The treatment of patients with Chronic HCV has improved dramatically over the past few years.

We are now seeing sustained virological response rates of 54-59% (41-16% - genotype 1, 88% - genotype 2 & 3) It has been suggested with Peg-IFN alfa 2b that this could be increased to 61% (48%-genotype 1; 88% - genotype 2 & 3) if the ribavirin is weight based dosing with interferon.

PEG-INF alfa 2b(PEG) and Ribavirin (RBV) has recently been shown to have an improved sustained response rate over IFN alfa 2b(INF) and RBV. The improved response is related to the sustained levels of interferon and the weight basing of PEG. Protein pegylation does come with a price as the viral activity of

PEG is only 35% that of INF. It is hypothesized that a combination of the two drugs may offer high viral activity as well as sustained pressure on the virus and improve sustained response rates.

### Aim:

The aim of this study is to prospectively evaluate the use of a combination of PEG and INF, along with RBV in the treatment of patients with Chronic Active Hepatitis C in naïve genotype 1 patients and non-responders to at least six months of INF +/- RBV therapy.

### Methods:

Patients eligible for the study receive PEG at 1.0ug /kg SQ every Saturday. INF is dosed at 3mil or 5mil units SQ every Monday, Wednesday, and Friday (0.5ug/kg/wk) and RBV is given at doses of 12-15 mg/kg/day.

Ribavirin dose adjustments are based on standard treatment practices of the treating physician. IFN dose adjusted for an ANC <750,000 or for platelets <50,000. The use of epoetin alpha and GCSF is permitted in protocol. Quantitative viral load levels obtained pre-treatment and at 12 weeks. A level is drawn at 24 weeks if the 12-week level was still positive.

Patients with persistence of HCV RNA at 24 weeks will be considered non-responders and treatment discontinued at that point. Initial responders will complete 48 weeks of therapy. A qualitative HCV RNA will be checked at week 72 on all initial responders to assess sustained response.

All the patients in the non-responder groups have completed 72 weeks and sustained response rates are available.

Treatment duration is for 48 weeks unless HCV RNA is detectable at 24 weeks.

### Results:

Results: A total of 35 patients (10 non-responders. and 25 Naive) have been enrolled in the study thus far and 34 patients have been on treatment for at least 12 weeks and have HCV RNA levels for analysis.

#### **Non-responders**

- ◆ Six of 10 (60%) of patients had biopsy proven cirrhosis
- ◆ Seven of these patients had genotype 1
- ◆ Nine (90%) had been non-responders to combo – interferon plus ribavirin
- ◆ Eight patients (80%) were initial responders to therapy
- ◆ Three (30%) went on to be sustained virological responders
- ◆ Of the SVR group two of the three had failed combo treatment
- ◆ Two of 4 patients without cirrhosis were sustained responders

#### **Naïve genotype 1 patients**

- ◆ Ten of 25 patients (40%) have high viral load
- ◆ Sixteen patients are male (64%)

#### **Naïve genotype 1 patients**

- ◆ Initial response rates data is available on 24 of the 25 patients
- ◆ Sixteen (67%) had undetectable HCV RNA
- ◆ At 12 weeks 20 (83%) had undetectable HCV RNA at 24 weeks
- ◆ There did not appear to be any difference between high viral load and low viral load

## Dose reductions

- ◆ Three of 34 patients (9%) required dose reductions of interferon
- ◆ Eight of 24 patients (24%) have had their ribavirin doses reduced

### Conclusion:

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The combination of PEG/INF/RBV in the schedule and doses outlined above can be given safely. Initial response rates to PEG/INF/RBV combination therapy in this difficult to treat patient population are very good and are better than those reported for PEG/RBV. Initial response rates do not insure sustained response rates (SRR). More patients need to be enrolled and sustained response rates need to be obtained in order to draw firm conclusions on its superiority. If these results persist and SRR are high, this could be a method to maximize the effects of interferon in the treatment of this difficult patient population. A large multicenter prospective randomized controlled study comparing PEG/RBV with PEG/INF/RBV in the above patient populations should be performed to see if there is a clinically significant difference in response rates.

## Abstract 1605

### Impact of Treatment On Liver Fibrosis In Autoimmune Hepatitis and Chronic Hepatitis B

*Reza Malekzadeh, Mehdi Mohamadnejad, Siavosh Nasser-Moghaddam, Nasser Rakhshani, Seyed Mohamad Tavangar, Amir Ali Sohrabpoor, Soosan Tahaghoghi, Shahin Merat, Nasser Kamalian*

### Background:

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Impact of treatment on fibrosis progression in autoimmune hepatitis (AIH) and chronic hepatitis B (CHB) is unknown. We assessed the changes in liver fibrosis before and after treatment in these two conditions.

### Methods:

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Fourteen AIH and 20 CHB patients who had paired liver biopsies were enrolled. Six AIH patients were treated with cyclosporine-A for 6 months followed by prednisolone and azathioprine, the rest were treated with prednisolone and azathioprine (median: 2.9 years). Patients with CHB had received lamivudine (median: 1.4 years). Before treatment, the fibrosis progression rate per year (FPR) was estimated as the ratio between fibrosis stage in Modified Hepatitis Activity Index (1 U, 1 stage; 6 U, cirrhosis) and the duration of disease before treatment. Post-treatment FPR was calculated by dividing the observed difference between stages by the interval between biopsies.

### Results:

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Median interval between biopsies was 2.97 and 2.98 years in patients with AIH and CHB respectively. Median fibrosis stage decreased from 4.07 to 2.35 in patients with AIH ( $P=0.002$ ). In CHB patients fibrosis stage decreased with treatment but it was not statistically significant (3.15 vs. 2.55;  $P=0.156$ ). Median FPR in AIH decreased from 5.728 U/year to -0.779 U/year ( $P<0.001$ ). Median FPR in CHB decreased from 0.472 U/year to -0.145 U/year ( $p=0.04$ ). Median FPR before treatment was significantly higher in AIH than CHB (5.728 vs. 0.472 U/year;  $P<0.001$ ). Median fibrosis regression rate post-treatment was significantly higher in AIH than CHB (-0.779 vs. -0.145 U/year;  $P<0.05$ ). In AIH patients, fibrosis worsened in 1 (7%), improved in 9 (64%), and remained unchanged in 4 (29%). In all 6 AIH patients who were treated with cyclosporine-A, fibrosis improved post-treatment. The use of cyclosporine-A was associated with improvement of fibrosis in AIH ( $P=0.02$ ). Among 20 patients with CHB, fibrosis worsened in 5 (25%), improved in 10 (50%), and remained unchanged in 5 (25%).

### Conclusion:

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Liver fibrosis progression before treatment and fibrosis regression after treatment is more rapid in AIH than in CHB. A 6 months course of cyclosporine-A followed by prednisolone and azathioprine may improve fibrosis better than prednisolone and azathioprine in AIH.

## **Abstract 1610**

### **Is There Any Relation Between CD81 Polymorphisms, HCV and the Presence of Cryoglobulinemia?**

*Supriya Joshi, Joshua Schimmer, Elizabeth J. Heathcote, Robert Rottapel*

#### ***Background:***

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Mixed cryoglobulinemia (MC) is a complication of chronic hepatitis C virus (HCV) infection--detectable in 50% of HCV patients, but only 1% of patients with HCV have symptomatic cryoglobulinemia. Symptoms may include cutaneous, purpura, arthritis and neuropathy and may predispose to lymphoproliferative disorders. Entry of HCV into hepatocytes and B lymphocytes may result from binding to CD81, a nonglycosylated tetraspanin protein that is widely expressed and involved in immune regulation, B cell stimulation, cell to cell interaction, and neuro-signaling.

#### ***Objective:***

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To determine if polymorphisms in the CD 81 coding region exist and may be correlated with decrease in laboratory manifestations of cryoglobulinemia. Polymorphisms in the CD81 coding region may predispose patients with HCV to the development of mixed cryoglobulinemia.

#### ***Methods:***

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Forty-three patients with HCV were selected for investigation. Patients with HCV +/- laboratory and clinical evidence of mixed cryoglobulinemia. 34 patients with hepatitis C were examined as well as 16 HCV negative healthy controls (HC). A retrospective chart review assessed patient demographics, manifestations of MC, cryocrit, liver histology, genotype and viral load when available. Lymphocytes were collected from fresh blood samples and RNA was isolated. RT-PCR was used to create a cDNA library for each patient and the CD81 coding region was amplified by PCR, inserted into the pCR<sup>®</sup> 2.1 TOPO<sup>®</sup> vector and transformed into competent 1-shot E. coli bacteria. Four clones from each patient were selected for CD81 sequencing and reproducible mutations were identified.

#### ***Results:***

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Sequence analysis was completed for 59 individuals, 16 HC, 9 HCV+/MC- and 34 HCV+/MC+, 22 (64.7%) of whom were symptomatic. Nucleotide aberrancies were found in 5 pts, 4 HCV+/+MC (12%), 0 HCV+/-MC (0%) and 1 HC (6%). Manifestations of MC included 1 skin, 1 renal, 1 skin/neuropathy, 1 skin/renal and 1 skin/renal/arthritis. No patient had overt lymphoma. Of the 5 patients with a CD81 polymorphism, 4 had changes in the coding sequence for the second extracellular region of the protein, to which HCV is reported to bind. However, of those 5 patients, 3 had DNA changes that did not correspond with a change in amino acid coding.

#### ***Conclusions:***

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- ◆ Polymorphisms of CD81 may predispose to the development of MC in patients infected with HCV.
- ◆ As 3 out of 5 polymorphisms did not result in amino acid substitution.

- ◆ 2 polymorphisms did not rise to amino acid changes
- ◆ The frequency of CD 81 polymorphisms in the human population and in the HCV affects cohorts will require the analysis of larger sample sizes
- ◆ Polymorphisms in CD 81 may affect disease susceptibility in HCV patients

## **Abstract 1611**

### **Lifestyle and Genetic Risk Factors for Progression of Hepatitis C**

*Sara H. Olson, Nancy Lau, Sandy Iyer, Daniel Egan, Irene Orlow, Jay Cowan, Temima Markovits, Robert C. Kurtz, Marianne Berwick*

#### ***Introduction:***

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In patients with hepatitis C, previous studies have indicated that risk factors for progression and hepatocellular carcinoma (HCC) include male gender, older age, and older age at infection. Some studies have reported slower progression in blacks than in whites. Individual differences in genes that are involved in the process of inflammation may also affect progression. We studied these and other potential risk factors in a hospital-based study in NYC. Our interviewers approach people in the clinics at Memorial Sloan-Kettering and North General Hospitals, obtain informed consent, administer a questionnaire, and collect mouthwash specimens for DNA. Participants fill out questionnaires on diet, family history, and quality of life. This analysis reports on 116 patients for whom data on stage based on liver biopsy were available, and includes 24 with hepatocellular carcinoma (HCC). Based on the questionnaire, we estimated route of infection (transfusion, intravenous drug use (IVDU), or other route), age at infection, and length of time infected. We studied the association of these variables, as well as age, gender, race, and GSTM1 genotype (null or present) with stage of disease. Stage of disease was dichotomized into early (stage 0, I, II, n=58) and late (stage III, IV or HCC, n=58). In univariate analysis, older age, higher number of years infected, infection at later ages (twenties or older), and infection through IVDU were significantly associated with increased risk of higher-stage disease. Odds ratios (ORs) were 6.3 for age  $\geq 60$ ; 2.6 for infected  $\geq 35$  years; 2.6 if infected in ones 20s vs earlier; and 2.6 if infected by IVDU. Older age remained a significant risk factor in all multivariate analyses and was a stronger factor than number of years infected or age at infection. Adjustment for age increased the strength of the association for IVDU (OR=5.0). Gender and race were not significantly associated with stage. With stratification by age, however, male gender increased risk among younger patients (OR=5.3), but not among older patients (OR=1.2). In addition, risk associated with IVDU was higher among younger patients (OR=7.6) than among older patients (OR=1.9). Patients who had the null genotype of GSTM1 were at higher risk, with an odds ratio of 2.4 ( $p=.04$ ) after controlling for race. The number of patients with higher-stage liver disease is likely to increase as the infected population ages and as IVDU becomes a more prevalent mode of infection. Differences in genes involved in inflammation may affect individual risk.

#### ***Background:***

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4 million people in the United States are infected with hepatitis C and are at increased risk for cirrhosis and hepatocellular carcinoma (HCC). Progression of disease widely varies among individuals. We are studying risk factors for progression including genetic susceptibility in a hospital-based case controlled study in New York City.

#### ***Method:***

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##### ***Study Participants***

- ◆ Patients at Memorial Sloane Kettering Cancer Center or North Central Hospital
- ◆ Positive for HCV by PCR

- ◆ > or = 18 years of age
- ◆ Able to speak English

### **Data Collection**

- ◆ Questionnaire to determine route of infection and risk factors for progression; administered by interviewer
- ◆ Diet history (Block96Brief)
- ◆ Quality of Life (QOL) – SF-36
- ◆ Family history of cancer
- ◆ Mouthwash specimen for genotyping

### **Data Analysis**

- ◆ 116 patients of whom we had data on stage based upon liver biopsy
- ◆ Includes 24 patients with hepatocellular carcinoma (HCC)
- ◆ Assigned route of transmission based on responses to questionnaire
- ◆ Estimated age of infection and length of time infected by questionnaire
- ◆ Compared those with earlier stage (0, I, II, n=58) to those with late stage (III, IV) or HCC n=58
- ◆ Results of genotyping available on a subgroup of respondents

### **Results:**

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**Age, age infected and length of time infected**-Older age at interview or at diagnosis of HCC was a strong risk factor for late stage liver disease. The age at infection or length of time infected had less influence. In multivariate analyses, we adjusted separately for gender, race and route of infection. Being > or = 60 years of age at interview or diagnosis remained strongly associated with risk after adjustment.

**Gender**-Men were at slightly elevated risk of later stage liver disease in our study population. Male gender was a strong risk factor among younger patients, but not among older patients.

**Route of Injection**-People infected by injection drug use compared to other routes were at somewhat increased risk of late stage liver disease. This effect was stronger after adjustment for age. The effect of injection drug use was stronger among younger patients.

**Genetic Susceptibility**-Patients who were null for GSM-1 were at increased risk of later stage liver disease. As expected genotype was associated with race; among blacks, 25% had the null genotype, compared to 52% among whites. The association with later stage remained after adjustment for race.

### **Conclusions:**

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The number of patients with higher stage liver disease is likely to increase as the infected population ages and as IVDU becomes a more prevalent mode of infection. Genetic variation may influence risk of progression.

## **Abstract 1613**

### **Safety, Tolerability And Efficacy Of Interferon Alfa 2b And Ribavirin Combination Therapy In HCV Patients With Cirrhosis**

*Ravi Ravinuthala, Vosudesh Pai, Dilip Moonka, Kimberly Brown*

### **Introduction and Purpose:**

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HCV infected patients with advanced liver disease are high risk for treatment with combination therapy with Interferon and Ribavirin due to tolerability and safety issues. However, successful treatment halts progression of the disease and reduces risk of HCC, but limited data is available. We report our experience in treating this high risk group.

### Materials and Methods:

Patients attending the Henry Ford Liver Center, Detroit, MI with cirrhosis or severe bridging fibrosis on liver biopsy were included in this study. All patients received standard combination therapy with Interferon 3 MU thrice-a-week and ribavirin 1000 or 1200 mg twice a day depending on the weight where possible. Side effects, laboratories were monitored monthly and dose was modified if necessary. Hemopoietic growth factors were used only if deemed necessary by the treating physician. HCV RNA was checked at the end of six months, one year and 18 months. Treatment was stopped if HCV RNA was positive at 6 months of treatment. If negative at 6 months, treatment was continued for 12 months. End of treatment response (ETR) was defined as negative HCV RNA at 12 months of treatment and sustained viral response (SVR) meant negative HCV RNA at 18 months.

### Results:

62 patients were included in the study. 2 (3%) patients did not complete the treatment due to side effects and were excluded from final analysis. 69% were Caucasian and 31% were African American. Male to female ratio was 7:3 (68% male; 32% female). Age ranged from 33-69 with a mean of 49.5. Cirrhosis was present in (50%) and (40%) had bridging fibrosis on biopsy. All patients were clinically Child's A class at the time of treatment although some had decompensation in the past. Majority were genotype 1. Platelet count ranged from 48,000-402,000 with a mean of 161,000 and mean viral load was 664395 I.U. Dosage reduction was required in 9 (15%) patients and erythropoietin was required in 2 patients. Two (3%) of patients did not complete the study due to adverse events. ETR was seen in 24 (39%) with SVR in 13 (23%). SVR in previous non responders was 61% as compared with 16% in naive patients.

### Summary/Conclusions:

- ◆ Male gender and African American race were associated with poor sustained response rates.
- ◆ SVR in patients previously treated with interferon was higher than the total group.
- ◆ Sustained response, discontinuation and dose reduction rates compare favorably with published literature.
- ◆ Combination therapy in patients with advanced fibrosis appears safe and well tolerated
- ◆ Prospective controlled trials are needed to establish the long term benefits in patients with viral clearance.

## **Abstract 1614** **Severity of Liver Disease in HCV Infected Dialysis Patients Awaiting Renal Transplantation**

*Renee Pozza, Else Albanese, Karel Biando, Erik Wahlstrom, Tarek Hassanein*

### Background:

Hepatitis C viral infection (HCV) is common in patients with end stage renal disease. 20-40% of patients on hemodialysis are infected with HCV. In 1997, 0.7% of patients receiving renal transplantation in the U.S. were positive for HCV antibodies. HCV viremia and disease activity is expected to increase as a result of immune suppression post-renal transplantation. Liver histology is crucial in evaluating patients for transplantation to avoid post-transplantation liver decompensation and failure.

## ***Aim:***

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The aim of this study is to identify severity of liver disease in HCV infected patients undergoing evaluation for renal transplant. Additionally this study will determine if HCV infected patients are candidates for renal transplantation by identifying the extent of their liver disease.

## ***Methods:***

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- ◆ Studied subjects with ESRD who were on dialysis undergoing evaluation for renal transplantation. All subjects were seropositive for anti-HCV
- ◆ Liver injury test, viral load by PCR and HCV genotype were obtained for all patients during the transplant evaluation
- ◆ Liver biopsies were scored for degree of fibrosis and extent of inflammation using the Metavir score
  - Stage 0 – No fibrosis
  - Stage 1 – Mild fibrosis (fibrous portal tracts)
  - Stage 2 – Moderate fibrosis (early septa)
  - Stage 3 – Severe fibrosis (portal-portal or portal-central bridging)
  - Stage 4 – Cirrhosis (bridging fibrosis/regenerative nodule formation)

## ***Results:***

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- ◆ 25(57%) were males and 19(43%) were female.
- ◆ Mean age was 52.4 years (range 24-72 years).
- ◆ 25% Caucasian, 34% Hispanic, 21% African American, 11% Asian, 7% Native American and 2% other.
- ◆ 84% were on hemodialysis while 16% were on peritoneal dialysis.
- ◆ 72% of patients have a viral titer <1 million copies/ml and 17% >1 million copies/ml using the superquant assay.
- ◆ 11% of the patients were HCV-RNA negative by PCR. 72% were genotype 1a/1b, 12% 2b, 12% 3a and 4% were genotype 4.
- ◆ The mean ALT and AST levels were 61 and 40 iu/dl respectively.
- ◆ Histologically 3% had severe inflammation, 40% had moderate inflammation and 57% had mild inflammation.
- ◆ Fibrosis scores were 0,1,2,3,4, in 31%, 36%, 11%, 17% and 5% respectively.
- ◆ Iron staining was positive in 89% of the biopsies. Severe iron deposition was seen in only 14% of the patients.
- ◆ All patients were considered candidates for renal transplantation.

## ***Conclusion:***

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Patients with ESRD on dialysis have mild histological disease. 0% of our cohort had advanced disease while 71% had mild and 29% had moderate disease. Therefore a liver biopsy is essential in evaluating HCV infected patients for renal transplantation. Since HCV disease progression is relatively slow even with immunosuppression, the majority of HCV-infected patients in our cohort were candidates for renal transplantation.

## **Abstract 1616**

### **The ?32 Mutation of the Chemokine-receptor 5 Gene is Neither Correlated with**

## **Chronic Hepatitis C nor Does it Predict Response to Therapy with Interferon-a and Ribavirin**

*Juergen Glas, Helga-Paula Torok, Christian Simperl, August Koenig, Katja Martin, Folkhard Schmidt, Martin Schaefer, Christian Folwaczny*

### ***Background:***

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As opposed to patients infected with HIV, homozygosity for a 32 bp deletion (?32) of the chemokine-receptor 5 (CCR5) gene was recently described in increased frequency in patients with chronic hepatitis C. Thus, it was speculated that this mutation might be relevant for disease susceptibility and influence the response to antiviral therapy. While a protective effect of this homozygous mutation against HIV infection is widely accepted, its role in hepatitis C is not yet clear.

### ***Aim:***

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The present study sought to confirm the association between chronic hepatitis C and the ?32 mutation of the CCR5 gene and to correlate it with the response to therapy with interferon-a-2a and ribavirin.

### ***Methods:***

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62 patients with chronic hepatitis C and 119 healthy unrelated controls were genotyped for the ?32 mutation by PCR and agarose gel electrophoresis. For the correlation between the ?32 mutation and response to therapy only patients (n=59) who completed six months of combination therapy as part of a prospective study were evaluated.

### ***Results:***

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The ?32 mutation was not observed in increased frequency in chronic hepatitis C. Furthermore, a significant difference concerning the viral load or aminotransferase values was not observed in carriers versus non-carriers of the ?32 mutation. After stratification for potentially confounding factors such as gender or HCV-genotype a significant difference was also not detected with respect to treatment outcome.

### ***Conclusions/Comments:***

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These observations argue strongly against a role of CCR5 for susceptibility to chronic infection with HCV or response to combination therapy with interferon-a-2a and ribavirin. However it has to be taken into account that our results are solely based on viral load and ALT value whereas data concerning histopathology and sustained virological response rates are lacking.

## **Abstract 1618 Effect of a Low Iron Diet in Chronic Hepatitis C**

*Tomoko Katoh, Kazutomo Suzuki, Hiroshi Takada, Gordon Luk, Hajime Kuwayama*

### ***Background and Aims:***

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Excessive hepatic iron deposition contributes to the progression of liver disease in hemochromatosis; and plasmapheresis or iron chelation are the mainstay of therapy. It is unclear whether excessive iron deposition may also contribute to progression of other chronic liver diseases, such as hepatitis C, and whether a low iron diet alone may be therapeutic. We therefore investigated the effect of a low iron diet in chronic hepatitis C.

## ***Methods:***

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In a preliminary study, we measured serum alanine transaminase (ALT) and ferritin levels in 111 patients with chronic hepatitis C. The effect of a low iron diet was studied in 23 of these patients who did not use alcohol and did not have previous gastric surgery (8 male and 15 female, 62+/-10 years old); and compared to 53 patients not on a special diet. Individual patient consulted their nutritional status for 6 months. By face to face interview patients were asked to change iron-rich food to another one. We measured serum ALT and ferritin levels, albumin (ALB), hemoglobin (Hgb), and red blood cell count (RBC).

## ***Results:***

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1. Serum ferritin levels in chronic hepatitis patients were significantly higher than those in the health subjects
2. Serum ALT was higher in patients with high ferritin levels than those with normal or low ferritin levels
3. Serum ALT levels were decreased by a low iron diet
4. Serum ferritin levels were decreased by a low iron diet
5. Low iron diet was very useful in 40% of patients (normalized ALTs) in chronic hepatitis C
6. No remarkable changes were noted in nutritional parameters such as hemoglobin and albumin

## ***Conclusion:***

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A low iron diet appears to be safe and effective in patients with chronic hepatitis C, and may be an alternative treatment option in patients who do not respond to or are not candidates for interferon therapy.

## **Abstract 1621**

### **Prevalence of Hepatitis C Virus (HCV) Infection in Non-Hodgkin's Lymphoma (NHL). Systematic Review and Meta-analysis**

*Javier P. Gisbert, Ml Garcia-Buey, Jm Pajares, R. Moreno-Otero*

## ***Aim:***

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To conduct a systematic review of studies evaluating HCV prevalence in B-cell NHL (B-NHL), and to perform a meta-analysis of case-control studies comparing this prevalence with a reference group.

## ***Methods:***

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All studies evaluating HCV prevalence in patients with B-NHL were considered. Studies comparing HCV prevalence in B-NHL (cases) and in a reference group (controls) were included in the meta-analysis. Bibliographical searches were conducted in several electronic databases. Prevalence (weighted mean) of HCV infection was calculated. Meta-analysis was performed combining the Odds Ratios (OR).

## ***Results:***

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Fifty studies (including 5,632 patients) evaluating HCV were identified, with 13% mean prevalence of infection (95%CI: 12-14%). This figure was higher in countries as Italy (20%) and Japan (16%). Ten studies compared HCV prevalence in B-NHL (17%) and in blood donors or healthy subjects (1.5%) (OR: 10.8; 95% CI: 7.3-16), results being homogeneous. OR increased up to 14.1 when only Italian and Japanese studies were considered. Sixteen studies compared HCV prevalence in B-NHL (13%) and other haematological malignancies different from B-cell NHL (2.9%) (OR: 4.2; 95%CI: 2.5-7), also without heterogeneity. This figure increased up to 7.5 when sub-analysis included only the Italian studies.

## ***Conclusion:***

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HCV prevalence in patients with B-NHL is approximately 15%, higher than that reported not only in general population (1.5%) but also in patients with other haematological malignancies (2.5%), suggesting a role of the virus in the aetiology of B-NHL. The striking geographical variation in this association suggests that genetic and/or environmental factors are also involved in the pathogenesis of this disorder.

## **Abstract 1622**

### **Racial Differences in Treatment Response to Hepatitis C Virus in a Large Urban Health System**

*John Riopelle, Lisa Forman, Sharon Bahrych, Katherine Doll, Neil Toribara*

#### ***Background:***

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Minority populations are disproportionately affected by hepatitis C virus (HCV), with estimated seroprevalences of 2.1% in Hispanics, 3.2% in African-Americans, and 1.3% in whites. Several studies have reported that African-Americans do not respond to treatment of chronic HCV infection with the same efficacy as Whites. To our knowledge no published study has evaluated the response rate of Hispanics to HCV treatment. Because our institution (Denver Health Medical Center, Denver, CO) serves a predominantly minority population - 52% Hispanic, 13% African-American and 25% white - we are uniquely positioned to investigate this question.

#### ***Methods:***

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We retrospectively reviewed all patients who completed treatment for HCV in our institution from January 1, 2000 until October 31, 2002. Data regarding self-reported demographics and virologic response were obtained via retrospective electronic chart review. HIV-positive patients and those with Childs class B or C were either not treated or excluded from analysis. Patients received several different regimens of interferon and ribavirin for either 24 weeks (non-genotype 1) or 48 weeks (genotype 1). Those with an end treatment sustained virologic response (SVR) returned at 6 months for follow-up viral load.

#### ***Results:***

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Fifty of 68 patients who began treatment finished the intended duration of therapy. The racial distribution of this group was 57.4% white, 30.9% Hispanic, and 7.4% African-American.

White and Hispanic groups had similar age and genotype 1 distribution (63% v. 61.1%). Gender distribution revealed a male:female ratio of 2:1 in whites and 1:2 in Hispanics.

#### **Sustained virological response rates**

- ◆ Total – (25/68) – 36.8%
- White (16/39) – 41%
- Hispanic (8/21) – 38.1%
- There were no sustained responders in the African American group

#### ***Conclusion:***

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- ◆ The preliminary data suggests that, in our patient population, Hispanic and white patients have similar rates to HCV treatment.
- ◆ Minority populations are underrepresented in HCV diagnosis and treatment groups compared to

Denver Health's racial distribution and the expected prevalence of HCV from large population studies like NHANES

- ◆ Prospective studies with standard treatment regimes are necessary to assess present standard of care and treatment response.

## **Abstract 1625**

### **The Rate of Treatment of Hepatitis C in Patients Co-infected With HIV in an Urban Medical Center**

*Alexander Restrepo, Timothy C. Johnson, David Widjaja, Lonny Yarmus, Kevin Meyer, Henry C. Bodenheimer Jr., Albert D. Min*

#### ***Introduction:***

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Hepatitis C virus (HCV) and HIV co-infection is a common clinical scenario because of shared risk factors. HIV significantly worsens liver disease in HCV infected patients, with a higher rate of progression and shorter time interval to development of cirrhosis than in patients without HIV. Successful treatment and eradication of the virus with interferon-based therapy reduces the morbidity and mortality of HCV infection. However, the applicability of the currently available treatment in the co-infected population in a community setting is unknown.

#### ***Objective:***

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Our objective was to determine the rate of treatment of hepatitis C in a HCV/HIV co-infected population in an urban medical center. Methods: We conducted a retrospective study of HCV/HIV co-infected patients consecutively evaluated at the liver/GI clinics at Beth Israel Medical Center for treatment of HCV during a 12 month period from July 2001 to June 2002. The patient characteristics and the decision to treat or not were recorded. Reasons for non-treatment were noted.

#### ***Results:***

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One hundred four co-infected patients were identified. Of these, 77 (73%) patients were males. The mean age was 48 years (range 32-72). Seventy-four of the 83 (89%) patients whose risk factor for HCV infection was known had a history of intravenous drug use. Overall, 21 (20%) patients had liver biopsy performed. Fourteen (67%) of those who had a liver biopsy were treated.

- ◆ Of the total group, 16 (15%) patients were treated.
- ◆ Ninety three patients were not treated for the following reasons:
  - 13 refused treatment
  - 30 were non-compliant with visits during the evaluation period
  - 11 were actively abusing alcohol and/or intravenous drugs
  - 10 had decompensated cirrhosis
  - 6 had a significant active psychiatric condition precluding treatment
  - 23 had significant co-morbid disease precluding treatment.

#### ***Conclusions:***

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A majority of patients co-infected with HCV/HIV seen at our urban liver/GI clinics had a history of intravenous drug use. Most co-infected patients were not considered to be candidates for interferon-based treatment of HCV. Educating patients about the importance of treatment and improving patient compliance during the pretreatment evaluation period may have a significant impact on the rate of treatment in these co-infected

patients.

## **Abstract 1626**

### **The Role of Helicobacter Pylori Infection on the Natural History of HCV and the Impact on the Response to Therapy**

*Maher Azzouz, Christopher J. Christensen, Gagan Sood*

#### ***Introduction:***

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Helicobacter Pylori infection (H. Pylori) plays an established role in both peptic ulcer disease and lymphoma. Many recent studies have implicated chronic infections with organisms such as H. Pylori, Chlamydia, and CMV on many chronic inflammatory states and neoplastic processes. Patients with chronic hepatitis C Virus (HCV) infection have increased prevalence of H.Pylori infection.

#### ***Objective:***

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The possibility of an abnormal immune state due to chronic H. Pylori could theoretically impact the natural history of HCV and response to treatment.

#### ***Methods:***

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We retrospectively evaluated a group of patients with chronic HCV from our clinic from July 1999 to June 2002 with and without H. Pylori in regards immune status, liver pathology and response to treatment. Seventy-five patients with chronic HCV infection were enrolled in the study. 56% of these patients were H. Pylori serum antibody negative and 44% were positive. Sixty of the total patients underwent treatment with antiviral therapy. Data collected and compared on the two groups included race, sex, age, BMI, serum ferritin level, Immunoglobulin G (humeral immunity) and response to PPD. Each patient also underwent liver biopsy and the two groups were compared regarding degree of inflammation and fibrosis on biopsy.

#### ***Results:***

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H. Pylori infection was found to be more prevalent in African American patients with HCV with a probability of  $p=0.0004$ . Also of statistical significance, it was discovered that the patients with chronic HCV who were serum H. Pylori positive had a lesser degree of fibrosis (mean  $1.27 \pm 1.2$ ) versus H. Pylori negative ( $1.95 \pm 1.48$ ). There was no statistically significant difference in mean IgG levels, PPD response, age, sex, or ferritin level in the two groups. Response to antiviral therapy was also not impacted by the H. Pylori status.

#### ***Conclusions:***

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- ◆ Our preliminary findings suggest a decreased degree of fibrosis in HCV patients co-infected with H. Pylori and show no association with co-infection and response to antiviral therapy. A larger sample size and further studies involving other inflammatory and immune markers may reveal the role H. Pylori infection has in chronic HCV infection and its treatment.

## **Abstract 1628**

### **Is Hepatitis C Genotype a Major Determinant in The Decision to Perform Liver Biopsy in Patients with Chronic Hepatitis C?**

*David Stokesberry, Muhammad K. Hasan, David M. Thompson, Aura Parra, Sikandar A. Mesiya*

### ***Purpose:***

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Appropriate clinical practice regarding management of chronic hepatitis C continues to evolve. Pre-treatment hepatitis C genotype determines treatment duration and predicts response rate. Liver biopsy is the most reliable test to assess the disease activity and prognosis. However, recent National Institute of Health recommendations have questioned the routine need for liver biopsy in patients with genotypes other than type 1.

This study surveyed gastroenterologists and hepatologists to establish the relative importance and weight given to hepatitis C genotype in formulating the decision to recommend liver biopsy.

### ***Methods:***

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A 15 question, two-page questionnaire was mailed to 3891 randomly selected members of the clinical practice section of the American Gastroenterology Association. Differences in means and response proportions were analyzed with t-tests and chi-square tests, respectively.

### ***Results:***

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311 of 3891 (34%) surveys were returned. Ninety-three percent of the respondents were general gastroenterologists and 7% were hepatologists. Seventy one percent were in private practice, 16% in academics and 13% were both. Eighty percent of the respondents surveyed advocate liver biopsy for patients with chronic hepatitis C. Seventy six percent of them recommend biopsy regardless of the genotype. The presence of non-1 genotype prompted 18% of respondents to be negatively disposed to recommend liver biopsy while 6% of respondents viewed this result as a positive factor in recommending liver biopsy.

Academic gastroenterologists were more likely than private practice gastroenterologists to defer liver biopsy in patients with non-1 genotype (26% versus 17%  $p=0.0071$ ). Similarly, hepatologists recommend fewer liver biopsies in patients with non-1 genotype as compared to general gastroenterologists (30% versus 19%  $p=0.0046$ ). Practices that see greater numbers of patients with hepatitis C are strongly associated with a decreased likelihood to advise biopsy in non-1 genotype patients ( $p<0.0001$ ).

### ***Conclusions:***

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The majority of surveyed private gastroenterologists currently advise liver biopsy for chronic hepatitis C regardless of the genotype. The decision not to recommend liver biopsy in non-1 genotype subjects was significantly higher in respondents who had an academic affiliation, sub specialized in hepatology or devoted a large proportion of their practice to treat hepatitis C.

It is unclear if those that don't recommend liver biopsy changing practice patterns based in genotype or simply clinical preference. Future studies may be needed to determine the necessity of liver biopsy in various subsets of patients with chronic hepatitis C.

### **Abstract 12603**

### **Combining INF alfa 2b with PEG-INF alfa-2b and Ribavirin in the treatment of Non-responders to previous therapy and Nieve Genotype 1 patients with Chronic Active Hepatitis C.**

*Scott M. Gioe*

## ***Introduction:***

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PEG-INF alfa 2b(Peg Intron) and Ribavirin (RBV) has recently been shown to have an improved sustained response rate over IFN alfa 2b(INF) and ribavirin. The improved response is related to the sustained levels of interferon and the weight basing of PEG. Protein pegylation does come with a price as the viral activity of PEG is only 35% that of INF. It is hypothesized that a combination of the two drugs may offer high viral activity as well as sustained pressure on the virus and improve sustain response rates.

## ***Aim:***

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The aim of this study is to prospectively evaluate the use of a combination of PEG and INF, along with RBV in the treatment of patients with Chronic active hepatitis C in naive genotype 1 patients and non-responders to at least six months of interferon plus ribavirin therapy.

## ***Methods:***

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Patients eligible for the study receive PEG at 1.0ug /kg SQ every Saturday. Interferon is dosed at 3mu or 5 mu SQ every Monday, Wednesday, and Friday (0.5ug/kg/wk) and ribavirin is given at doses of 12-15 mg/kg/day.

Treatment duration is for 48 weeks unless HCV RNA is detectable at 24 weeks.

## ***Results:***

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A total of 35 patients (10 non-responders and 25 Naive) have been enrolled in the study thus far and 29 patients have HCV RNA levels that are available for analysis. HCV RNA is undetectable in 25/29 (86%) patients. Of the non-responders, 8/10 (80%) became HCV RNA negative on treatment. Nineteen of the twenty-five naive genotype 1 patients have completed at least 12 weeks and 17/19 (89%) have undetectable HCV RNA.

Dose reductions of PEG/INF were required in 2/35 (6%) patients. Six patients out of 35 (17%) have required dose reductions in RBV. No serious adverse events have been noted so far.

## ***Conclusion:***

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The combination of PEG/INF/RBV in the schedule and doses outlined above can be given safely. Initial response rates to PEG/INF/RBV combination therapy in this difficult to treat patient population are very good and are better than those reported for PEG/RBV.

Initial response rates do not insure sustained response rates (SVR). More patients need to be enrolled and sustained response rates need to be obtained in order to draw firm conclusions on its superiority. If these results persist and SVR are high, this could be a method to maximize the effects of interferon in the treatment of this difficult patient population. A large multicenter prospective randomized controlled study comparing PEG/RBV with PEG/INF/RBV in the above patient populations should be performed to see if there is a clinically significant difference in response rates.