

Digestive Disease Conference: Day Three

Alan Franciscus
Editor-in-Chief, HCV Advocate



[Print this page](#)

Abstract 504

Pegylated interferon alfa-2b plus ribavirin in patients with chronic hepatitis C: A trial in prior nonresponders to interferon monotherapy or combination therapy and in combination therapy relapsers: Final Results.

Abstract 505

Epoetin alfa Treatment of Anemic HCV-infected Patients Allows for Maintenance of Ribavirin Dose, Increases Hemoglobin Levels, and Improves Quality of Life Vs Placebo: a Randomized, Double-blind, Multicenter Study

Abstract 1204

Effect of Silybum Marianum on Serum ALT and Well Being in Chronic Hepatitis C

Abstract 1206

Pegylated Interferon alpha 2b (PEG-IFN) plus Ribavirin (RBV) versus Pegylated Interferon alpha 2b for Chronic Hepatitis C in HIV Patients

Abstract 1207

A Preliminary Study of Growth Factors Versus Dose Reduction for Peg Interferon Alfa-2b and Ribavirin Associated Neutropenia and Anemia in HIV/HCV Co-Infected Patients.

Abstract 1208

Non-Invasive Assessment of Fibrosis Resolution/Progression in Chronic Hepatitis C Patients Who Received Anti-Viral Therapy

Abstract 1209

Safety and efficacy of pegylated interferon (peg INF)-alfa-2b plus ribavirin (RBV) for the treatment of chronic hepatitis C in HIV-coinfected patients: 48 week results.

Abstract 1210

Treatment With Pegylated Interferon Alpha 2B and Ribavirin Produces Significant Sustained Virologic Response Rates in HCV Infected Patients who Failed Prior Therapy

Abstract 1214

Interleukin-11 In Patients With Chronic Hepatitis C And Advanced Liver Disease Who Have Been Nonresponsive To Antiviral Therapy

Abstract 1215

Early Virologic Response to Interferon and Ribavirin Treatment in Patients Co-infected with Hepatitis C Virus and Human Immunodeficiency Virus

Abstract 1216

Retreatment with Pegylated Interferon-Alpha2b Plus Ribavirin in Patients with Chronic Hepatitis C Not Responding to a Previous Antiviral Treatment with Standard Interferons Combined with Ribavirin

Abstract 1217

Study in CHC Patients Comparing Three Different Combination Therapies with Interferon a-2b (IFN) and Ribavirin (Rebetol): Weekly PEG-IFN (Peg- Intron) Versus Daily IFN (Intron A Pen) Versus Standard Regimen of IFN (Intron A Pen).

Abstract 1218

Effect of therapy with pegylated interferon-alpha 2b on platelet activation and apoptosis in patients with chronic hepatitis C.

Abstract 1219

Efficacy of Daily Interferon in Combination with Ribavirin in Patients with Chronic Hepatitis C: Final Results of A VA Multicenter Study

Abstract 1220

Early Viral Kinetics in Chronic Hepatitis C Virus Genotype 4 Infection

Abstract 1221

Safety and Efficacy of Peginterferon Alpha-2b plus Ribavirin in Pre-Cirrhotic and Cirrhotic Patients with Chronic Hepatitis C

Abstract 1222

An Open Prospective Study of Adacolumn Granulocyte and Monocyte/Macrophage Adsorptive Apheresis in Combination with Interferon-Alpha and Ribavirin in 6 Refractory Patients with High Plasma HCV Viremia

Abstract 1223

High Dose Paroxetine and Quetiapine to Augment Interferon and Ribavirin Treatment in Chronic Hepatitis C Patients With Psychiatric Disease

Abstract 1225

Pilot Study of Interferon Gamma for Chronic Hepatitis C

Abstract 1226

Thrombocytopenia (T) in Patients with Chronic Hepatitis C: Management with Interleukin 11

Abstract 1246

Treatment of Acute Hepatitis C Virus with Recombinant Interferon Alpha 2b. Clinical Trial

Abstract 1256

Biopsy vs. Non-Biopsy: A Comparison of Cost of Treatment of a Biopsy vs. Non Biopsy Model in the Management of HCV Prisoners

Abstract 1258

The Role of Triple Therapy with Amantadine Sulphate Plus Ribavirin and Interferon-Alpha2a on Chronic Hepatitis C Patients

Abstract 1259

Hepatitis A Prevalence in Intravenous Drug Users and Blood Product Infected Hepatitis C Patients.

Abstract 1262

Mutagenic effect of ribavirin in NS5A and NS5B regions and response to interferon/ribavirin combination therapy in patients with chronic hepatitis C

Abstract 1267

Abstract 1269

Steatosis as a Predictive Factor for Treatment Response in Patients with Chronic Hepatitis C

Abstract 1272

Nonlinear HCV and linear ALT Dynamics in serum during high dose Interferon

Abstract T1274

The Potential to Increase the Number of Hepatitis C Patients Receiving Treatment.

Abstract 1275

Predictive factors for dose modification and premature discontinuation of interferon plus ribavirin for adverse effects in Japanese patients with chronic hepatitis C

Abstract 1278

African Americans Failing Treatment with Interferon Monotherapy for Chronic Hepatitis C Are Less Likely to Achieve Sustained Response to Subsequent Retreatments Compared to Caucasians.

Abstract 1279

A combined therapy with high dose of interferon (IFN)-alpha as an induction and ribavirin in non-responders to IFN alone with chronic hepatitis C

Abstract 1280

Triple Combination of Pegylated Interferon Alpha 2b, Ribavirin and Amantadine for Treatment of Chronic Hepatitis C

Abstract 1283

Treatment of HCV-Related Mixed Cryoglobulinemia with Interferon and Ribavirin

Abstract 1284

Study of Hepatitis A Virus Superinfection to Hepatitis C Patients

Abstract 1285

Incidence of High Depressive Symptoms in Chronic Hepatitis C (CHC) Patients Following Interferon Plus Ribavirin Therapy.

Abstract 1286

Differential Response Rates to Clearance of Hepatitis C Virus in Chronic Hepatitis C, Based on Racial Makeup of Patients Treated With Interferon/Ribavirin (I/R) or Peg/Ribavirin (Peg/R) Combination

Abstract 1287

Efficacy of Hepatitis C treatment is a function of ethnicity

Abstract 1289

Patient's Misconceptions Regarding The Hepatitis C Virus Before And After An Educational Class

Abstract 1292

PEG-Interferon a-2b + Ribavirin for Treatment of Patients with Chronic Hepatitis C Who Have Previously Failed to Achieve a Sustained Virologic Response Following Interferon alfa or Interferon a-2b + Ribavirin Therapy.

Abstract 1293

Pegylated Interferon Alfa 2b and Ribavirin for Hepatitis C Patients Who Were Nonresponders to Previous

Abstract 504

Pegylated interferon alfa-2b plus ribavirin in patients with chronic hepatitis C: A trial in prior nonresponders to interferon monotherapy or combination therapy and in combination therapy relapsers: Final Results.

Ira M. Jacobson, Furqaan Ahmed, Mark W. Russo, Robert S. Brown Jr., Edward Lebovics, Albert Min, Stephen Esposito, Norbert Brau, Hillel Tobias, Franklin Klion, Edmund Bini, Neil Brodsky, Deborah Rovner, Clifford Brass, NY PEG-Intron Study Group

Background:

Pegylated interferon (PEG IFN) has proven superior to standard interferon (IFN) as monotherapy for chronic hepatitis C and, more recently, in combination with ribavirin (RBV) in treatment naive patients.

Aim:

To compare the efficacy of two dose regimens of peginterferon alfa-2b plus ribavirin in patients with prior nonresponse to IFN monotherapy or combination therapy, or with relapse after combination therapy. We present final data from this study.

Methods/Patients:

Patients in the three categories were randomized to receive:

- (1) Peginterferon alfa-2b 1.0 μ /kg plus RBV 1000-1200 mg/d (Group 1), or
- (2) Peginterferon alfa-2b 1.5 μ /kg plus RBV 800 mg/d (Group 2).

Prior therapy must have been stopped at least three months prior to entry. Three hundred twenty one patients were treated for 48 weeks with cessation of therapy if HCV RNA PCR (Roche Amplicor) was positive at 24 weeks.

Fibrosis scores—stage 2, group 1-18%; group 2-14% (p=ns); stage 3-4, group 1-5%; group 2-24% (p=0.03)

Results:

Of 321 patients enrolled in the study, 161 were randomized to Group 1 and 160 were randomized to Group 2. Overall, the sustained response (SR) rate was 15% across the three categories. SR rates for the different treatment groups are given in the table. Among the combination nonresponders, patients with genotype 1 had lower SR rates than non-genotype 1 patients (5-9% vs. 13-25%). Patients with normal ALT respond as well as those with an elevated ALT at onset of therapy (21% vs. 14%, p=0.54).

Patients with advanced fibrosis (Metavir stage 3-4) tend to do respond better with the higher dose of PEG IFN (25% vs. 5%, p=0.44)

Conclusions:

- ◆ SR rates are highest in combination relapsers (range 32-47%) and lowest in genotype 1 combination nonresponders (range 5-9%).
- ◆ Breakthrough and relapse are more common than in naive patients; the concept of treatment for more than 12 months warrants further study.
- ◆ Higher dose of PEG IFN may be better in patients with fibrosis.

- ◆ Normal ALT does not adversely affect response.
- ◆ Lower treatment response results in African Americans than other groups

This study is supported by Schering-Plough Corporation.

Quantitative PCR <1000 cop/ml at follow-up week 24

	Week 24	Week 48	SVR
Comb NR- Group 1	20/114 (18%)	12/114 (11%)	7/114 (6%)
Comb NR- Group 2	31/105 (30%)	23/105 (22%)	10/105 (10%)*
Comb Rel- Group 1	18/25 (72%)	13/25 (52%)	8/25 (32%)
Comb Rel- Group 2	24/30 (80%)	23/30 (77%)	14/30 (47%)*
IFN NR- Group 1	10/22 (45%)	7/22 (32%)	6/22 (27%)
IFN NR- Group 2	13/25 (52%)	10/25 (40%)	4/25 (16%)*
93% of Comb NR were genotype 1. *p>0.05 Group 1 vs. Group 2			

Abstract 505

Epoetin alfa Treatment of Anemic HCV-infected Patients Allows for Maintenance of Ribavirin Dose, Increases Hemoglobin Levels, and Improves Quality of Life Vs Placebo: a Randomized, Double-blind, Multicenter Study

Nezam H. Afdhal, Douglas T. Dieterich, Paul J. Pockros, Eugene R. Schiff, Mitchell L. Shiffman, Mark S. Sulkowski, Teresa Wright, Zobair Younossi, Peter J. Bowers

Background:

Combination therapy for chronic HCV infection is ribavirin (RBV)/interferon a (IFN) or RBV/pegylated IFN a (PEG-IFN)—induces anemia that may compromise the ability to achieve a sustained virologic response (SVR) by prompting RBV dose reduction or cessation. Treatment (tx) adherence is critical for achieving an sustained virological response, and studies suggest that maintaining higher RBV doses (1000/1200 mg/day vs 800 mg/day) is more effective (*Hadziyannis et al., EASL. 2002; Manns et al., Lancet. 2001; McHutchison, Hepatology. 2000*).

We assessed whether epoetin alfa (EPO) treatment of anemic (Hb ≤12 g/dL) HCV-infected patients (pts) could maintain RBV dose, increase hemoglobin (Hb) levels, and improve quality of life (QOL).

Methods:

HCV patients (N=186) who developed anemia while being treated with RBV/IFN or RBV/PEG-IFN for an anticipated period of ≥16 weeks were randomized to receive 40,000—60,000 IU, SC QW epoetin alfa or matched placebo (PL) with titration for 8 wks (double-blind phase [DBP]).

Following the double-blind phase, eligible patients received open-label epoetin alfa for the remainder of their HCV therapy. After HCV therapy cessation, patients were followed at 4, 12, and 24 weeks. The primary efficacy endpoint (assessed at the end of week 8) was RBV dose success—a week 8 RBV dose ≥study entry RBV dose. Secondary efficacy endpoints assessed at Weeks 9 and 17 were RBV dose, change in Hb levels, and QOL self-assessments (Linear Analog Scale Assessment [LASA] and Medical Outcomes Study Short Form-36v2 [SF-36v2]).

Results:

By week: Patients (n=95 [EPO], n=92 [PL]) had similar baseline (BL) characteristics. RBV dose success was achieved in 82 patients (88%) of patients on epoetin alfa versus 50 patients (60%) on PL (P<.001). Mean RBV doses at the end of the double blinded DBP were 944 ± 217 mg/day (EPO) and 855 ± 241 mg/day (PL)

($P < .001$). At 8 wks, 80% of EPO-treated pts had a RBV dose = the dose at the start of HCV therapy vs 49% of pts on PL ($P < .0001$). Mean Hb levels at the end of the double blinded phase were 13.0 ± 1.3 g/dL (EPO) vs 10.8 ± 1.0 g/dL (PL) ($P < .001$); mean changes from BL Hb were $+2.2 \pm 1.3$ g/dL (Epoetin) and 0 ± 1.0 g/dL (PL). Mean scores on the LASA and selected SF-36v2 domains improved significantly from BL with EPO vs PL ($P < .001$ — $.003$). Epoetin alfa appeared safe and well tolerated.

Conclusions:

In anemic HCV-infected patients on RBV/IFN or RBV/PEG-IFN, EPO maintains RBV dose and significantly improves anemia and QOL. Epoetin alfa has the potential to improve adherence rates, which may in turn improve sustain virological response rates.

Abstract 1204

Effect of Silybum Marianum on Serum ALT and Well Being in Chronic Hepatitis C

Adam Gordon, Daryl A. Hobbs, Andrew J. P. Francis, Stuart K. Roberts

Introduction:

Chronic hepatitis C (CHC) often causes significant morbidity in subjects via fatigue and impaired quality of life (QOL). Silybum marianum is a herbal preparation commonly used by subjects with CHC. However, limited information is available on its efficacy in improving liver chemistries and symptoms.

Aim:

Thus, the AIMS of this study are to assess the efficacy and safety of 600mg and 1200mg of silybum marianum on ALT levels and well being in patients with CHC.

Patients and Methods:

We enrolled 24 subjects with CHC into a randomized, double-blinded, placebo-controlled, cross-over study. Subjects received 12 weeks of both silybum (either 600mg or 1200mg/d) and placebo given in random order across the cohort, with treatment periods separated by a 4 week washout interval. Subjects were followed for 12 weeks after the second treatment phase. Baseline biochemical, virological, psychological and QOL Short Form 36 (SF36) tests were performed. Biochemical tests were repeated monthly, and QOL assessments were repeated at the end of both treatment periods. ALT results were blinded to subjects and clinicians during the study. Comparisons were made using the Student t test and χ^2 analysis.

Results:

16 patients completed the trial, including 10 male subjects and 10 (63%) subjects with genotype 1 infection; this reflects the distribution of CHC in the Australia. The mean total SF36 score increased with silybum therapy compared to baseline (73.7 ± 19.4 v 60.6 ± 17.6 ; $p = 0.003$) but not compared to placebo ($p = 0.74$). Mean scores for individual SF36 domains and anxiety did not differ significantly between silybum and placebo. The mean ALT after treatment with silybum was not significantly different compared to placebo ($87\text{U/L} \pm 36$ v $103\text{U/L} \pm 60$; $p = 0.10$) and baseline levels ($97\text{U/L} \pm 46$). Also, the mean change in ALT on silybum was not significantly different compared to placebo ($+5\text{U/L} \pm 32$ v $+5\text{U/L} \pm 57$; $p = 0.98$). Three patients on silybum and 4 on placebo achieved a 25% reduction in ALT. The frequency of adverse events was similar with silybum and placebo ($p = 0.24$). No significant adverse events occurred and no significant differences were seen with daily doses of 600mg and 1200mg silybum.

All P values=not significant

Change in liver chemistries in placebo and silybum marianum

Parameter	? Placebo	? <i>S. marianum</i>	P value
ALT (u/l)	4 ± 57	6 ± 32	.90
Bilirubin (mol/l)	0 ± 1	-1 ± 3	.057
SGT (IU/l)	8 ± 27	- 3 ± 21	.09
ALP (U/L)	-1 ± 13	-4 ± 17	0.26

Conclusion:

Silybum is safe and well tolerated in subjects with chronic hepatitis C. However, silybum does not significantly affect QOL, anxiety or ALT values compared to placebo, and hence appears to have little efficacy in CHC, but does result in a significant increase in STAI S-anxiety score.

Abstract 1206

Pegylated Interferon alpha 2b (PEG-IFN) plus Ribavirin (RBV) versus Pegylated Interferon alpha 2b for Chronic Hepatitis C in HIV Patients

Antonietta Cargnel, Elena Angeli, Annalisa Mainini, Guido Gubertini, Riccardo Giorgi, Giovanna Orlando, Piergiorgio Duca, Italian Coinfection Study Group ICOS

Background:

- ◆ In HIV positive patients chronic hepatitis C has an aggressive course, and mortality for end stage liver disease is growing
- ◆ The introduction of highly active antiretroviral therapy (HAART) has improved the life expectancy of HIV infected individuals
- ◆ In these conditions, treatment of chronic hepatitis C in co-infected patients becomes crucial
- ◆ Little data is available concerning the use of PEG-IFN plus ribavirin in HIV/HCV coinfecting patients
- ◆ Because of the complexities of HAART, drug-drug interactions can occur

Objective:

- ◆ To study the efficacy and tolerability of PEG-IFN plus ribavirin versus PEG-IFN alone

Methods:

- ◆ HIV-HCV patients were randomized in an open, prospective, multi-center study
- ◆ Inclusion criteria were: stable HIV-RNA <400 cp/mL and CD4+ cells > 300 cells/mm³
- ◆ Clinical and laboratory monitoring were performed at regular intervals.

Treatment Schedule:

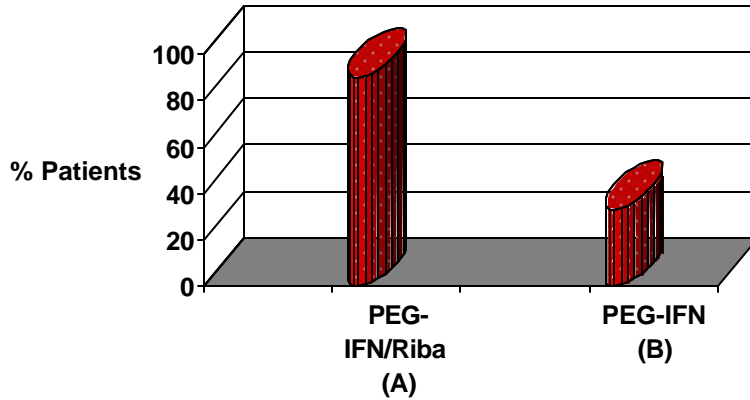
- ◆ PEG-IFN 1.5 µg/kg qw plus ribavirin 800 mg/daily – Group A
- ◆ PeG-IFN 1.5 µg/kg qw – Group B

Baseline characteristics

	PEG-IFN/ Riba (A)	PEG-IFN (B)
Gender	55 males 14 females	57 males 9 females
Age	39 (31-61)	38 (22-65)
HIV Epidemiology: IVDU	51	58

Sexual Not available	14 4	7 1
Mean CD4+ cell/mm ³	566 (300-1448)	617 (307-1429)
Mean ALT	142 (22-1000)	143 (24-543)
Mean HCV-RNA (log ₁₀ IU/mL)	5.9	5.9
Genotype 1/3; 2/3	37;32	31;33

Interim data 48 weeks



48 weeks

Virological response (negative PCR) in 12 patients (63.2%); 9/10 patients (90%) treated with PEG-IFN/RBV, 3/9 (33.3% with PEG-IFN; Fisher's exact test $p=0.019$)

Kinetics of HCV-RNA: 6th/12th Month of Treatment

- ◆ A drop of more than 2 logs of HCV-RNA at month 2 is significantly related to virological response at month 6 ($p=0.0004$ Fishers exact test) and at month 12 ($p=0.0018$ Fisher's exact test)

Potential Factors Influencing the Response to Anti-HCV Therapy

	Responders (24 weeks)	Non-Responders (24 weeks)	
Mean age	38.8	37.7	n.s
Male/Female	22/4	38/8	n.s
IVDU/Others	20/6	38/8	n.s
Genotype 1, 4	7	30	P=0.0029
Genotype 2,3	19	16	
ECA	26	34	P=0.0199
Cirrhosis	0	8	
Mean CD4+ (cells/mm ³)	599	138	n.s
Mean ALT (IU/mL)	168	138	n.s
Mean HCV-RNA(log ₁₀ IU/mL)	5.9	6	n.s

Toxicity and Tolerability (1):

- ◆ CD4+ cell/mm³ decreased at week 24 (group A: 600 → 453; group B: 621 → 491 cells/mm³); an increase (2 log) of HIV RNA was observed in 2 patients
- ◆ Therapy was discontinued in 51 (37.7%) patients, mostly during the first month (28/52 → 54.9%) without a significant difference between the groups (group A: 29/69; group B: 22/66, $p = 0.37$)
- ◆ Reason for discontinuation were
 - Trial violation (11 patients)
 - Side Effects (33 patients, 24.4%)

- Compliance (7 patients)

Toxicity and Tolerability (2):

- ◆ PEG-IFN dose was reduced in 19 patients (14%) and RBV in 7 patients (10.1%)
- ◆ The most frequently observed adverse events included: hematologic toxicity (11.8%), flu-like syndrome (8.9%), psychiatric disorders (2.9%), cutaneous rash (1.5%)
- ◆ Three patients had a significant increase in ALT levels after 24 weeks of therapy; for one patient, it was related to the introduction nevirapine (NVP) in antiretroviral therapy.
- ◆ Neither life threatening adverse events nor severe lactic acidosis occurred, independently from HAART regimen

Conclusion:

- ◆ Preliminary results indicate that PEG-IFN plus ribavirin appears to be a promising choice for HIV/HCV coinfecting patients
- ◆ The high percentage of study discontinuations may be related to low awareness of early adverse events or lack of motivation of patients to continue treatment. Counseling is extremely important to improve compliance.
- ◆ A drop of more than 2 logs of HCV –RNA after 8 weeks seems to be predictive of virological response at 24 and 48 weeks, but this finding needs to be confirmed by further results.

Abstract 1207

A Preliminary Study of Growth Factors Versus Dose Reduction for Peg Interferon Alfa-2b and Ribavirin Associated Neutropenia and Anemia in HIV/HCV Co-Infected Patients.

Preeti Golia, Andrew H. Talal, Ira M. Jacobson, Sandra Flynn, Piyush Golia

Background:

HIV/HCV co-infection is a major cause of liver-related morbidity and mortality. Pegylated interferon (IFN-a) and ribavirin (RBV) are commonly associated with neutropenia and anemia, leading to discontinuation in up to 27% of co-infected patients.

Aim:

We prospectively evaluated the safety of Peg IFN -a-2b/RBV and compared two management strategies for the treatment of medication-associated anemia and neutropenia in co-infected patients.

Methods:

Twenty-one HCV/HIV co-infected, therapy-naive subjects with hemoglobin (hgb) levels of ≥ 11 mg/dL and absolute neutrophil counts (ANC) $\geq 1,200/\text{mm}^3$ were treated with Peg-IFN a-2b 1.5mcg /kg/wk and RBV 13 2 mg/kg/day. Safety and tolerability were evaluated at Weeks 1, 2, 4, and monthly until Week 48 with serial CBC, CD4 T-cell counts, HIV and HCV RNA levels. Subjects whose hgb was ≤ 10 mg/dL were randomized to either receive recombinant human erythropoietin (epoetin alfa) 40,000 U/wk (Group A, n = 13) or RBV dose reduction to 10 mg/kg/d (Group B, n = 7). Subjects whose ANC was ≤ 750 cells/mm³ were randomized to either receive Granulocyte-Colony Stimulating Factor (G-CSF) 5 mg/kg/d BIW (Group A, n = 7) or to Peg-IFN dose reduction to 1.0 mcg/kg/wk (Group B, n = 3).

Results:

Twenty-one (17 male) patients with a mean age of 47.0 (range = 36 - 60) years, who have been followed for a mean of 20 (range = 6 - 42) weeks, had a baseline mean hgb = 14 mg/dL and mean ANC = 1935/mm³. During the study, one subject withdrew consent on day 5, an additional subject was withdrawn secondary to refractory anemia, and two subjects secondary to refractory neutropenia. At Week 4, 13/20 patients had a mean hgb decrease of 2.8 +/- 0.75 mg/dL that declined by a mean of 3.5 +/- 0.76 mg/dL by Week 12. In Group A, 7/13 patients had a mean hgb increase from 8.9 mg/dL to 9.7 mg/dL (p = 0.03) while in Group B, 4/13 patients had a mean hgb increase from 9.9 mg/dL to 11.4 mg/dL (p = 0.02) within two weeks after the intervention. At Week 4, 10/20 patients had a mean ANC decrease of 1015/mm³ that declined by a mean of 1148/mm³ by Week 12. In Group A, 3/10 patients had a mean ANC increase from 571 to 1814/mm³ (p=0.15) while in Group B, 7/10 patients had a mean ANC increase from 553 to 2013/mm³ (p=0.16) within two weeks after the intervention.

The effect of dose reduction growth factor supplementation in therapeutic response (HCV RNA) will be determined upon study completion.

Results - Anemia

Characteristics:

- ◆ Developed at an average of eight weeks
- ◆ NADIR hgb at week 9
- ◆ Mean baseline hgb Group A: 13.6 mg/dl
- ◆ Mean baseline hgb Group B: 14.0 mg/dl

Mean hgb increase post 4 week of intervention

- ◆ Group A (11/18) 9.3 mg/dl to 10.6 mg/dl (P=.0003)
- ◆ Group B (5/18) 9.6 mg/dl to 11.1 mg/dl (P=.002)

Outcome

- ◆ Hgb response to each intervention dose does not differ significantly (P=0.29)

Results – Neutropenia

Characteristics

- ◆ Developed neutropenia at an average of 8.8 weeks
- ◆ NADIR ANC at week 12
- ◆ Mean baseline ANC Group A: 2,225 /mm³
- ◆ Mean baseline ANC Group B: 3,222 / mm³

Mean ANC increase post 3.6 weeks of intervention

- ◆ Group A (4/12) 600 to 2,806 / mm³ (P=0.16)
- ◆ Group B (5/12) 551 to 1,749/ mm³ (P=0.13)

Outcome

- ◆ ANC response to each intervention does not differ significantly (P=0.33)

Conclusion:

Anemia and neutropenia are common side effects of Peg-IFN and RBV treatment. Growth factor supplementation and dose-reduction are effective for the management of neutropenia and anemia in HIV/HCV co-infected individuals.

Abstract 1208

Non-Invasive Assessment of Fibrosis Resolution/Progression in Chronic Hepatitis C Patients Who Received Anti-Viral Therapy

Yasushi Shiratori, Haruki Yamada, Yusei Ikeda, Masayuki Matsumura, Naoaki Hashimoto, Ryo Nakata, Masao Omata

Introduction:

Liver fibrosis is a dynamic process, with phases of either net matrix deposition or net degradation leading, respectively, to progression or regression of fibrosis. Recently, there are several reports indicating that fibrosis of the liver regressed in patients with sustained virological response. Fibrosis progression was also retarded in patients who received interferon therapy (*Shiratori Y, Ann Intern Med 2000*). Fibrosis regression stage could be assessed by repeated liver biopsy, but liver biopsy sometimes induces serious event of bleeding or death. Thus, it may be benefit for the patients to assess fibrosis regression state using blood only.

Methods:

To evaluate the dynamics of fibrosis progression/regression in chronic hepatitis C patients, thirty-seven patients who received a daily administration of 6 to 10 million unit (MU) of interferon-alfa 2b thrice weekly for 24-26 weeks were enrolled.

PIIP levels, cytokines contributing to matrix production (PDGF, TGF-beta), and the enzymes regulating matrix degradation (MMP-1, TIMP-1) in serum were measured during therapy, at the completion of therapy, and 24, 48, and 72 weeks after the end of therapy.

Results:

When the patients were categorized according to sustained response state to interferon, PIIP levels was markedly decreased in sustained responders during treatment and after the end of treatment, while it was not decreased in the non-sustained responders. Both TGF-beta and PDGF levels were markedly decreased in sustained responders during IFN therapy and shortly thereafter, but these values in non-sustained responders were not changed after the end of therapy. Although MMP-1 level was not changed in sustained responders as well as non-sustained responders during treatment and after the end of treatment, TIMP-1 level in sustained responder was significantly reduced after the end of treatment and thereafter, while that in non-sustained responders was not changed.

Conclusion:

These results suggest that there is an increase in matrix degeneration process which may be associated with a decrease in the level of TIMPs. Once the source of liver injury could be removed, it is possible to restore effective extracellular matrix degradation even after the end of treatment. The present data may indicate that extracellular matrix degradation persists in sustained responders. By measuring these cytokines and enzymes, the process of degradation of matrix could be evaluated without liver biopsy.

Abstract 1209

Safety and efficacy of pegylated interferon (peg INF)-alfa-2b plus ribavirin (RBV) for the treatment of chronic hepatitis C in HIV-coinfected patients: 48 week results.

Esther Voigt, Christian Schulz, Gerd Klausen, Joachim Goelz, Stefan Mauss, Antonius Mutz, Franz A. Mosthaf, Elke Lauenroth-Mai, Juergen K. Rockstroh

Background:

The natural course of chronic hepatitis C is accelerated in HIV coinfecting patients. Therefore specific treatment strategies are urgently needed. We evaluated long term efficacy and safety of peg INF- α -2b plus RBV for treatment of HCV in HIV-coinfecting patients.

Methods:

Within this open label, uncontrolled, multicenter trial patients received peg INF 1.5 mug/kg plus 800 mg RBV per day over 48 weeks with HCV genotypes 1 or 4, and 24 weeks with genotypes 2 or 3. Quantitative HCV RNA, HIV RNA and CD4 cell count as well as blood count and liver enzymes were assessed at baseline and at weeks 4, 12, 24, 48. 105 patients have been enrolled so far. Follow up is still ongoing.

Results:

Here we present data on 52 patients who have completed 48 weeks. At baseline 52 patients (median age 38.5 years, range 23-58, 71% male, 62% i.v. drug users) showed a median HCV RNA of 5.93 log cps/ml (range 3.8-7.9). 52% were infected with HCV genotype 1, 33% with genotypes 2 or 3. Median HIV RNA was 326 cps/ml (range <50 to 76852 cps/ml), median CD4 cell count was 417/mul (range 150 to 1288/mul) at baseline, respectively.

Forty-eight percent of patients were receiving concomitant antiretroviral treatment. 23/52 patients (44%) showed an end of treatment response with HCV RNA below detection limit of 500 cps/ml, 26% of patients with genotype 1, compared with 87% with genotype 3.

Eight patients (15%) discontinued study treatment prematurely due to adverse events

- ◆ 4 due to psychiatric disorders,
- ◆ 2 due to blood count abnormalities.
- ◆ 21 (41%) patients discontinued due to virological non response.

CD4 cell count declined significantly at week 12 and 24. However, relative CD4 count remained stable as well as HIV RNA.

Conclusions:

Antiviral efficacy of peg INF plus RBV appears to be lower in HIV/HCV coinfecting compared with HCV mono-infected patients. Overall, discontinuation rate is low. However, psychiatric disorders are a major problem in this cohort with a high proportion of former drug users.

Abstract 1210

Treatment With Pegylated Interferon Alpha 2B and Ribavirin Produces Significant Sustained Virologic Response Rates in HCV Infected Patients who Failed Prior Therapy

Paul J. Gaglio, Melissa Brown, David Zimmerman, James Choi, Larry Heller, Robert Brown Jr.

Introduction:

Eradicating HCV in the majority of infected patients remains an elusive goal, particularly in previously treated patients who failed or relapsed following prior therapy. We hypothesize that response rates in these patients who are re-treated with Pegylated interferon and ribavirin will be improved compared to standard interferon preparations with or without ribavirin. The present prospective study is designed to determine the efficacy and safety of treatment with PEG-Intron (pegylated interferon α -2b) and ribavirin in a group of patients

who failed prior therapy with interferon with or without ribavirin.

Methods:

439 patients are presently enrolled in this multi-center study. The first 250 enrolled patients were treated with 1.5 mg/kg of PEG-Intron sc q week, and Ribavirin 800 mg po qd. The remaining patients received 1.5 mg/kg of PEG-Intron and weight based Ribavirin (800-1400mg). The intended duration of treatment is 48 weeks regardless of 24 week HCV RNA. 192 patients have been treated for at least 48 weeks and SVR data at week 72 is available in 98 patients, all treated with 800mg Ribavirin/d

Adverse Events:

Dose reduction was required in 22% of patients most commonly due to leukopenia and anemia. Permanent discontinuation of therapy was required in 8% most often due to: depression or anxiety

Serious Adverse Events:

(1.8% of 439 pts) Included one patient each with neutropenia/MRSA sepsis, optic neuritis with monocular blindness, perirectal abscess, cellulitis and multi-organ failure, cutaneous and pulmonary sarcoidosis, pneumonia, homicidal ideation, and suicide.

Conclusions:

- 1) Overall end of treatment response rate was 46% and the sustained virological response rate was 33%.
- 2) SVR was significantly higher in genotype non-1 patients and those who failed previous monotherapy
- 3) 15% of G1 non responders to Rebetron achieved a sustained virological response rate (16% Caucasian, 12% Black) 4).

It is hoped that a weight based dose of ribavirin will be associated with lower relapse rates and improved sustained response rates particularly in G1 patients.

<i>Study Entry (%)</i>	<i>Wk 48 (% HCV -)</i>	<i>Wk 72 (% HCV -)</i>
<i>Genotype 1 (83)</i>	44	32
<i>Genotype non 1 (17)</i>	70	50
<i>Previous Ifn/Riba (79)</i>	44	29
<i>Previous Ifn mono (21)</i>	60	50
<i>Genotype 1 combo NR (50)</i>	27	15

Abstract 1214

Interleukin-11 In Patients With Chronic Hepatitis C And Advanced Liver Disease Who Have Been Nonresponsive To Antiviral Therapy

Eric J. Lawitz, Thomas Casey, Norma S. Cantu

Background

Those with advanced liver disease as a result of Hepatitis C are at risk for decompensation requiring liver transplantation or the development of hepatocellular carcinoma. Immune mediated injury is the primary mechanism of injury resulting in hepatic inflammation and fibrogenesis. It has been shown that there is a positive correlation between both gamma interferon and Interleukin (IL)-2 mRNA expression and the severity of both hepatic inflammation and fibrosis. IL-11 decreases the TH-1 cytokines such as gamma interferon and IL-2 (Keith, Cytokine Reference 2000, 565). In the setting of psoriasis, IL-11 has been shown to

suppress the TH-1 response at doses as low as 2.5 mcg/kg/day, which is greater than ten fold lower than the currently approved dose for thrombocytopenia (Trepicchio, J Clin Invest 1999; 104(11),1527).

Aim

To evaluate the effect of IL-11 on the histologic activity index (HAI) in patients who have been nonresponsive to antiviral therapy yet have advanced liver disease.

Methods

A baseline liver biopsy was performed in those with advanced liver disease defined as a Metovir score of F3-F4. All participants were treated with rhIL-11 5.0mcg/kg/day subcutaneously daily for 3 months. At the completion of therapy a post therapy liver biopsy was performed. HCV-RNA was obtained at the initiation and completion of therapy.

Table 1. Baseline characteristics (N=20)

Age (mean)	50.5 years
Male/Female (%)	60/40
Weight (mean)	79.6 kg
HCV-RNA (mean)	5,595,600 copies/ml
HAI (mean)	7.0
Fibrosis stage 3 (%)	50
Fibrosis state 4 (%)	50

Results

Twenty adult participants with Metovir F3-F4 fibrosis with compensated liver disease were enrolled. The mean age is 50.5 years with a mean weight is 79.6 kg. Sixty percent were male. Mean baseline HCV-RNA 5,595,600 copies/ml. Mean baseline HAI is 7.0 with Metovir fibrosis scores of F3 in 50% and F4 in 50%.

Serum alanine transaminase (ALT) levels were found to decrease with administration of IL-11. In addition IL-11 caused an increase in platelets. Change in Knodell Histologic Activity Index (HAI) indicated that inflammatory activity was improved in 55% of patients. In 40% of patients, this improvement was significant. In only 10% of patients, inflammatory activity increased. Overall, IL-11 was well tolerated with no serious adverse events reported among patients. Lower extremity edema occurred in all patients but was not significant. One patient (5%) discontinued treatment because of extravascular fluid retention.

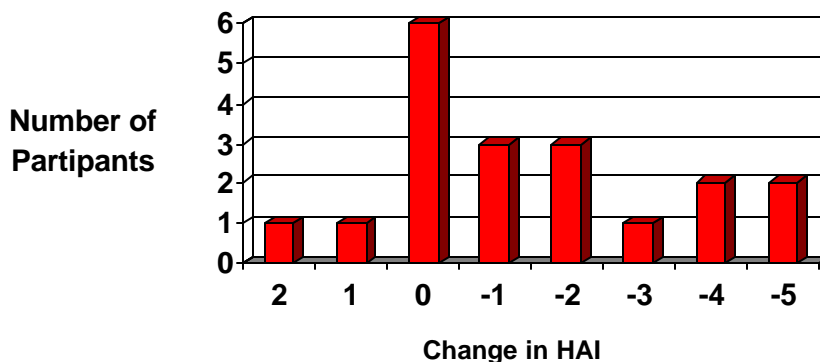


Figure 1. Change in HAI. Alternations in HAI indicated that inflammatory activity improved in 10% of patients, inflammatory activity increased.

Conclusion

IL-11 is well tolerated in patients with advanced liver disease. In most patients, inflammatory activity was improved, and in many patients this improvement was significant. Additionally, use of IL-11 caused ALT levels to decrease and platelets to increase. Further trials are needed to extend the duration of therapy and to evaluate the effect of IL-11 on fibrosis.

Abstract 1215

Early Virologic Response to Interferon and Ribavirin Treatment in Patients Co-infected with Hepatitis C Virus and Human Immunodeficiency Virus

Elana Maser, Ron Palmon, Douglas T. Dieterich

Background:

The prevalence of HCV infection in HIV patients ranges from 20-50%/ Patients with hepatitis C virus (HCV) infection who have a virologic response to interferon (IFN) and ribavirin (RBV) regimens usually respond within the first 12 weeks of therapy. We reviewed the virologic response rate to IFN and RBV regimens in patients co-infected with HCV and human immunodeficiency virus (HIV) who were predominantly HCV genotype 1.

Methods:

We conducted a retrospective chart review of 31 HIV/HCV co-infected patients from a New York City practice. All patients were treated with weight appropriate doses of IFN and RBV. The serum HIV and HCV RNA were detected using the polymerase chain reaction and were recorded approximately once per month.

Results:

- ◆ Patient Characteristics:
 - The majority of patients were HCV genotype 1 (74%) and male (84%).
 - Mean HCV RNA at baseline was 2,733,774 IU/ml.
- ◆ Treatment:
 - 71% of patients were treated with PEG-IFN/RBV and 29% with IFN/RBV.
- ◆ Baseline statistics:
 - At baseline, the median CD4 count was 425/microl., 64% of patients had undetectable HIV viral loads, and 68% were on highly active antiretroviral therapy.

The median duration of treatment was 39 weeks. Twelve of 31 patients (42%) had an end-of-treatment response (defined as the absence of detectable HCV RNA at cessation of therapy). Of those twelve responders, HCV RNA was <400 copies/ml in nine patients (77%) by week 12. Of the remaining three responders, two patients had a 2 log decrease in viral load within 12 weeks, and one had a 2 log decrease in HCV viral load by 24 weeks.

Conclusions:

In patients with predominately genotype 1 HCV and HIV infection, the response to therapy almost always occurs within 12 weeks. If patients do not have at least a 2 log decrease in HCV viral load by 12 weeks, discontinuation of therapy should be considered.

Abstract 1216

Retreatment with Pegylated Interferon-Alpha2b Plus Ribavirin in Patients with Chronic Hepatitis C Not Responding to a Previous Antiviral Treatment with Standard Interferons Combined with Ribavirin

Gerlinde Teuber, Birgit Kallinowski, Claus Niederau, Hans Klinker, Peter R. Galle, Myrka Zankel, Stefan Zeuzem

Introduction:

In interferon (IFN) non-responders with chronic hepatitis C, retreatment with standard interferons combined with ribavirin showed sustained virologic response rates of 20-30%. Only limited data is available concerning the efficacy of antiviral retreatment in patients not responding to a previous treatment with standard interferons combined with ribavirin.

Aims:

The aims of the present trial were to evaluate efficacy and safety of a retreatment with pegylated IFN- α 2b plus ribavirin.

Patients/Methods:

240 patients (162 males, 78 females, mean age 45.5 years) not responding to previous antiviral treatment with standard interferons combined with ribavirin.

Patients received pegylated IFN- α 2b 100 μ g/week s.c. for 8 weeks followed by 50 μ g/week s.c. for 40 weeks in combination with ribavirin 800 mg/d for 48 weeks.

Treatment was discontinued in patients with detectable serum HCV-RNA after treatment week 24.

Results:

A virologic end-of-treatment response was achieved in 25/240 (10.4%) patients while after a follow-up period of 24 weeks a sustained virologic response was observed in 15/240 (6.3%) patients.

Patients infected with HCV genotype non-1 were more likely to respond to antiviral retreatment than patients infected with HCV genotype 1 (6.8% vs. 17%).

Conclusions:

In conclusion, antiviral retreatment with pegylated interferon- α 2b plus ribavirin in this flat and low dose showed only a limited therapeutic efficacy in patients with chronic hepatitis C not responding to previous treatment with standard interferons and ribavirin. In these patients, virologic response rates may be improved by administering pegylated interferon- α 2b and ribavirin bodyweight adapted or by the addition of other antiviral agents

Abstract 1217

Study in CHC Patients Comparing Three Different Combination Therapies with Interferon α -2b (IFN) and Ribavirin (Rebetol): Weekly PEG-IFN (Peg- Intron) Versus Daily IFN (Intron A Pen) Versus Standard Regimen of IFN (Intron A Pen).

Introduction:

The combination of PEG-interferon a-2b and ribavirin is considered to be the standard treatment for naive chronic HCV patients.

Aim:

A study was initiated to compare the sustained virological response and safety of daily Intron A versus PegIntron, both in combination with Rebetol .

Patients/Methods:

Three hundred seventeen naive chronic HCV patients were randomized in three groups with a ratio of 2:2:1.

- ◆ Group A: daily interferon a-2b (4 MIU s.c. for patients > 65 kg or 0.06 MIU/ kg for patients < 65 kg) and ribavirin—130 patients
- ◆ Group B: PEG-interferon a-2b (100µg s.c. weekly for patients > 65 kg or 1.5µg/kg weekly for patients < 65 kg) and ribavirin—119 patients
- ◆ Group C (reference arm): interferon a-2b (3 MIU s.c. TWI) and ribavirin—68 patients

The duration of the treatment was 48 weeks for all 3 groups, with a 6 month follow-up period.

Results:

We are presenting the results of an interim analysis performed on the available patient data. Demographic data, PCR results and reasons for early withdrawal have been statistically analysed. At baseline, the 3 groups didn't show any statistical difference regarding age, gender, race, genotype and METAVIR score.

- ◆ At week 24 on treatment, HCV RNA (Amplicor) was undetectable in 86% in group A, in 80% in group B and in 67% in group C.
- ◆ At the end of treatment, 69% 70% and 55% respectively, had a negative PCR result.
- ◆ At week 24 of follow-up, these results were 60%, 52% and 29%, respectively.

When comparing the efficacy of the daily interferon (+ ribavirin) and the PEG-interferon (+ ribavirin) regimen, no statistical difference was found ($p = 0.378$).

78 patients withdrew before termination of the treatment:

- ◆ 30 patients in group A---43% due to adverse events
- ◆ 22 patients in group B—18% due to adverse events
- ◆ 26 patients in group C—19 due to adverse events

Regarding safety, no statistical difference was found for the drop-out rate in the daily interferon (+ ribavirin) regimen versus the PEG-interferon (+ ribavirin) arm ($p = 0.420$).

In contrast, a statistical higher rate of drop-out was observed in the old standard therapy (group C) versus group A ($p = 0.024$) and versus group B ($p = 0.004$).

Conclusion:

In conclusion, daily weight based Intron A dosing and PEG-Intron weighed based dosing once weekly both in combination with ribavirin offer the same efficacy and safety rates.

Abstract 1218

Effect of therapy with pegylated interferon-alpha 2b on platelet activation and apoptosis in patients with chronic hepatitis C.

Monika Homoncik, Wolfgang Sieghart, Wolfgang Jessner, Elisabeth Formann, Alfred Gangl, Peter Ferenci, Markus Peck-Radosavljevic

Objective:

Interferon alpha induced thrombocytopenia can become a limiting factor for therapy continuation. Platelet counts provide no information about platelet function. Quality of platelet function is crucial for the assessment whether a patient is at risk for bleeding or not. The present study was carried out to evaluate the effect of pegylated IFN-alpha administration on the expression of platelet activation markers and apoptosis in patients with chronic hepatitis C.

Methods:

10 patients with chronic hepatitis C (subtype 3a) received once a week 1 mcg/kg pegylated IFN-a2b (Peg-Intron (R), Schering, Vienna, Austria) subcutaneously over a period of 4 weeks, following by 180 mcg pegylated IFN-a2a once a week. Platelet counts, expression of P-selectin and GPIIb/IIIa receptor on platelets as markers of platelet activation and annexin V as a marker of apoptosis were measured by whole blood flow cytometry at baseline, day 1, day 3 and every other week over a period of 12 weeks.

Results:

Platelet counts dropped to a minimum of 70% of the baseline 4 weeks after begin of interferon therapy ($p < 0,01$). There were no significant changes in P-selectin, GP/IIb/IIIa receptor or annexin V expression on platelets during the study period ($p > 0,05$).

Conclusions:

Therapy with interferon alpha significantly decreases platelet count, but has no effect on platelet activation or apoptosis. Dose reduction or discontinuation of pegylated IFN-alpha due to moderate thrombocytopenia does not seem to be warranted based on our data regarding platelet activation but in vivo bleeding time was not assessed in this study. Apoptosis may not play an important role in the induction of IFN-alpha induced thrombocytopenia.

Abstract 1219

Efficacy of Daily Interferon in Combination with Ribavirin in Patients with Chronic Hepatitis C: Final Results of A VA Multicenter Study

Edmund J. Bini, Ayse Aytaman, Bhupinder S. Anand, Arun Samanta, Isabelita Cordoba-Rellosa, Bernard Nemchausky, Hector H. Trevino, Mitchell Mah'moud, Allan P. Weston, Neville R. Pimstone, Saray Stancic, Kyong-Mi Chang, Rosemary James

Background:

Hepatitis C is a major problem in U.S. veterans and the prevalence of infection is higher than non-veterans. Prior studies suggest that the SVR rates with IFN alpha and RBV may be lower than the general population. Furthermore, the optimal dose and duration of IFN + RBV therapy in this population is not known.

Aim:

The aims of this study were: 1) to determine the sustained virologic response to IFN alfa-2b (3 MU TIW) and RBV for 48 weeks in veterans with chronic HCV, 2) to evaluate whether 3 MU of daily IFN in combination with RBV for 24 weeks is superior to standard combination therapy, and 3) to determine the impact of HCV therapy on health-related quality of life (HRQOL).

Method:

158 IFN naive patients from 11 VA Medical Centers were randomized to receive either 3 MU of IFN alfa-2b QD plus RBV (1000 - 1200 mg/d) for 24 weeks (daily therapy group) or 3 MU of IFN alfa-2b TIW plus RBV (1000 - 1200 mg/d) for 24 weeks (genotype 2 & 3) or 48 weeks (genotype 1) (standard therapy group). HRQOL was measured using the Hepatitis QOL Questionnaire.

Results:

The proportion of patients with genotype 1 (78.2% vs. 80.0%, $P = 0.78$), number of patients with cirrhosis (10.3% vs. 10.0%, $P = 0.96$), mean HCV viral load (1.8 vs. 2.0×10^6 copies/ml, $P = 0.41$), and proportion of African American patients (26.9% vs. 35.0%, $P = 0.27$) did not differ significantly. The virologic response rates at the end of treatment in the daily IFN group were higher than in the standard group for all genotypes (46.2% vs. 23.8%, $P = 0.003$) and for those with genotype 1 (37.7% vs. 12.5%, $P = 0.001$), but did not differ for those with genotype 2 and 3 (76.5% vs. 68.8%, $P = 0.71$). Similarly, the sustained virologic response rates 24 weeks after treatment in the daily IFN group were higher than in the standard group for all genotypes (30.8% vs. 16.3%, $P = 0.03$) and for those with genotype 1 (19.7% vs. 6.3%, $P = 0.03$), but did not differ for those with genotype 2 and 3 (70.6% vs. 56.3%, $P = 0.48$). The proportion of patients who completed therapy did not differ between groups (82.1% vs. 80.0%, $P = 0.74$). Both daily and standard therapies were associated with significant improvements in several domains of HRQOL.

Conclusion:

The sustained virologic response to IFN alfa-2b 3 MU TIW and RBV in veterans with chronic HCV is lower than the response rates reported in non-veterans. Daily administration of 3 MU of IFN alfa-2b in combination with RBV for 24 weeks is superior to standard IFN alfa-2b 3 MU TIW and RBV for 48 weeks in veterans with genotype 1. In contrast, daily therapy was no better than standard therapy for patients with genotype 2 and 3. In our patient population, treatment with combination therapy was associated with significant improvements in HRQOL. Future studies to determine whether pegylated IFN + RBV can improve the SVR in veterans with chronic hepatitis C is warranted. This study was supported in part by a grant from Schering Plough Corp.

Abstract 1220

Early Viral Kinetics in Chronic Hepatitis C Virus Genotype 4 Infection

Wolfgang Jessner, Michael Gschwantler, Elisabeth Formann, Petra Steindl-Munda, Hanns Hoffmann, Christian Mueller, Peter Ferenci

Introduction:

In patients infected with hepatitis C virus (HCV) genotype 1, a decrease in HCV RNA levels of $< 0.8_{10}$ within 24 hours of a single dose of interferon alpha (IFN) predicts nonresponse to IFN/ribavirin with 100% specificity.

Similarly, a decrease in HCV RNA levels of $< 0.7 \log_{10}$ after a single 9 MU dose of IFN predicted nonresponse to peginterferon alfa-2a (40KD) plus ribavirin with 81% specificity in patients harboring HCV genotype 1. In contrast, the decrease in HCV RNA levels within 24 hours and 14 days after initiation of peginterferon alfa-2a (40KD) 180 µg/week, had no predictive value with respect to virological responses.

In common with genotype 1 infection, patients infected with HCV genotype 4 are considered “difficult-to-treat”, however, no data are available on the predictive value of the 24-hour virological response (24hVR) to IFN in patients infected with HCV genotype 4.

Objective:

Determine whether viral kinetic studies are of predictive value in HCV genotype 4 infection analogous to HCV genotype 1 infection.

Patients and Methods:

The study population comprised 33 consecutive, IFN-naïve patients with chronic hepatitis C infection attributable to HCV genotype 4. The population included 29 Egyptians and 4 Austrians. All patients were HCV RNA positive, had elevated ALT levels for = 6 months, and liver biopsy findings characteristic of chronic hepatitis C. HCV RNA levels were determined by COBAS AMPLICOR HCV MONITOR Test, v2.0, and COBAS AMPLICOR HCV Test, v2.0 (Roche Diagnostics). HCV genotypes were determined by line probe assay (Innogenetics N.V., Zwijnaarde, Belgium).

Patients received a single 10 MU dose of IFN on day-7 of the study. Between day 0 and 14, patients received IFN 5 MU/day. Subsequently, patients received combination therapy for 48 weeks comprised of FIN 5 MU three times weekly (n=6), PEG IFN alfa-2b 1.5 µg/kg/week (n=7), or peginterferon alfa-2a (40KD) 180 µg/kg/week (n=7) plus ribavirin 1 or 1.2 g/day.

Study End Points:

The primary end point was the virological response after 6 months of treatment with IFN/ribavirin or PEG IFN alfa-2B/ribavirin, or after 3 months of treatment with peginterferon alfa-2a (40KD)/ribavirin. Sustained virological responses as determined by qualitative PCR six months after completion of treatment was a secondary end point.

Result:

Patient characteristics according to virological response are presented in Table 1.

<i>Table 1. Patient Characteristics According to Virological Response After 3 or 6 Months of Treatment</i>		
	HCV RNA Negative (n=26)	HCV RNA Positive (n=7)
<i>Age (year)</i>	39 (21-51)	41* (30-50)
<i>Sex (M/F)</i>	24/2	5/2*
<i>Viral load (kIU/mL)</i>	267 (16.4-1190)	403* (125-783)
<i>ALT (IU/mL)</i>	41 (14-190)	58* (26-100)
<i>Weight (Kg)</i>	77 (61-93)	71* (61-102)
<i>BMI</i>	24.7 (20.7-30.4)	26.1* (21.1-32.2)
<i>Fibrosis score</i>	2 (1-4)	3* (1-4)

*Not Significant

The decrease in HCV RNA levels was more pronounced, both after a single IFN test dose and during 14 days of daily IFN therapy, in patients who achieved virological responses after 3 or 6 months of combination treatment, than in patients who did not achieve virological responses (Table 2)

	24 hours 10 MU IFN	24 hours 5 MU IFN	14 days 5 MU/day IFN
Responders (n=26)	1.37 (0.40-2.48)	0.99 (0.09-2.22)	2.4 (0.37-3.59)*
Nonresponders (n=7)	0.33 (0.08-0.57)*	0.16 (-0.12-0.46)*	0.16 (-0.13-0.74)*

*p = .0002 versus responders

The positive and negative predictive power of different tests is presented in Table 3.

Decrease in HCV RNA levels (time period) and dose of IFN	Sensitivity (d=7)	Sensitivity (d=26)	Positive Predictive Value	Negative Predictive Value
< 0.06 log ₁₀ (24-hr) after IFN 10 MU	100%	92.3%	77.8% *(d=9)	100% (d=24)
<0.5 log ₁₀ (24-hr) after IFN 5 MU	100%	88.5%	70% (d=10)	100% (d=23)
<0.8 log ₁₀ (14-day) after IFN 5 MU/day	100%	84.6%	63.6% (d=11)	100% (d=22)

d = denominator

The HCV RNA response after single and multiple doses of IFN according to virological responses are presented in Table 4.

	24 hours 10 MU IFN	24 hours 5 MU IFN	14 days 5MU/day IFN
Sustained virological responder (n=7)	1.54 (1.26-1.91)	1.17 (0.90-1.46)	2.86 (2.20-3.35)
Nonresponders (n=5)	0.44 (0.27-1.88)*	0.41 (0.13-1.77)**	0.43 (0.27-3.41)**

p=.062; ** p = 0.88

Summary:

- ◆ The 24-hour decline in HCV RNA levels after a single 10MU dose of IFN has a high predictive value for the outcome of subsequent combination therapy in patients infected with HCV genotype 4.
- ◆ A decrease of < 0.6 log₁₀ identifies nonresponders with a sensitivity of 92%.

Conclusions:

- ◆ Some patients with a poor response to IFN achieve on-treatment virological responses to pegylated IFN/ribavirin, although relapse is not uncommon after the end of treatment.
- ◆ Pretreatment prediction of sustained virological response may help select patients for antiviral treatment, although the concept must be confirmed in larger studies.

Abstract 1221

Safety and Efficacy of Peginterferon Alpha-2b plus Ribavirin in Pre-Cirrhotic and Cirrhotic Patients with Chronic Hepatitis C

Frederic Marrache, Marie Pierre Ripault, Yann Consigny, Dominique Cazals Hatem, Nathalie Boyer, Michele Martinot, Claude Degott, Dominique Valla, Patrick Marcellin

Background:

In patients with chronic hepatitis C, peginterferon alpha-2b (PEG-IFN) plus ribavirin (RBV) is the most effective therapy. However its benefit remains unclear in pre-cirrhotic and cirrhotic patients. This group is minority in clinical trials, and tolerance has not been specifically assessed, especially regarding to initial blood count abnormalities commonly observed in these patients.

Objective:

The objective of this study was to assess tolerance and efficacy of therapy with PEG-IFN plus RBV in unselected pre-cirrhotic and cirrhotic patients.

Methods:

74 patients were treated with PEG-IFN (1.5 or 1 microg/kg/week) plus RBV (800-1200mg/day). Tolerance and safety were evaluated by the rate of treatment's discontinuation, and occurrence of serious clinical adverse events, respectively. Virological response was assessed by detection of serum HCV RNA (Amplicor, Roche Diagnostics) at week 12, at the end and six months after treatment. Histological response was assessed on liver biopsy performed the last week of treatment.

Results:

Among 74 treated patients, 41 % had cirrhosis and 59% bridging fibrosis. Child-Pugh score was five in all patients except three with a score of six, and three with a score of seven. Platelet count was below $100 \times 10^9/L$ in 27 % and neutrophil count below $1.5 \times 10^9/L$ in 7 % of patients. No serious clinical event was observed. Treatment was withdrawn in 19% of patients. Dose reduction was necessary in 8% of patients for PEG-IFN and in 23% patients for RBV. In a multivariate logistic regression, initial blood count abnormalities were not associated with cessation of treatment. Treatment was discontinued because of blood count abnormalities in only two patients. Overall sustained virological response rate was 32 %. Details are shown in the table. End of treatment liver biopsy was performed in 23 patients. Eleven had baseline cirrhosis. Regression of fibrosis was observed in eight patients and reversion of cirrhosis in three.

Conclusion:

Combination therapy with peginterferon plus ribavirin for chronic hepatitis C seems safe and effective in patients with bridging fibrosis or compensated cirrhosis. Hematological tolerance is not a limiting factor.

Percentages of Patients with Undetectable HCV-RNA

	Naive		Previously IFN treated		Previously IFN plus RBV treated	
	Genotypes 1 or 4 n=13	Genotypes 2 or 3 n=15	Genotypes 1 or 4 n=14	Genotypes 2 or 3 n=7	Relapsers n=6	Non-responders n=19
End of treatment	23	87	50	71	83	21

(EOT)						
Six months after EOT	23	57	43	57	33	0

Abstract 1222

An Open Prospective Study of Adacolumn Granulocyte and Monocyte/Macrophage Adsorptive Apheresis in Combination with Interferon-Alpha and Ribavirin in 6 Refractory Patients with High Plasma HCV Viremia

Koji Sawada, Kunio Ohnishi, Ken Fukunaga, Tsuyoshi Kusaka, Yoshihiro Fukuda, Toshikazu Hada, Takashi Shimoyama, Abby Saniabadi, Ichiro Hirata

Objective:

Granulocytes and monocytes/macrophages are extra-hepatic sites for HCV replication and dissemination. This study was to investigate if granulocyte and monocyte adsorptive apheresis enhances the efficacy of INF-alpha and ribavirin combination therapy.

Methods:

Six patients, mean age 53.8 yr, range 46 to 65 yr were included. The inclusion criteria were chronic hepatitis and HCV-RNA greater than 100KIU/mL of genotypes 1b, 2a or 2b. Qualitative and quantitative analysis using Amplicor-PCR and alanine aminotransferase (ALT) were done to determine HCV-RNA level and liver function. All 6 patients were hitherto non-responders to a standard 24 week IFN-alpha therapy.

Leukocyte apheresis was done with Adacolumn which contains cellulose acetate beads as the adsorptive carriers for neutrophils and monocytes /macrophages; one session was 60 minutes at 30 mL/minute.

Interferon in combination with ribavirin was started after 5 consecutive Adacolumn sessions over 5 days. Daily 6 million units of IFN for 4 weeks and then every other day for 20 weeks were given together with ribavirin (600-800 mg/patient). Complete response (CR) was judged when plasma HCV-RNA did not become positive and liver function kept normal during the 6 months follow-up, without additional therapy. Partial response (PR) was judged when HCV-RNA became negative and liver function became normal during the therapy and then became positive during the follow-up.

Results:

All 6 patients completed the study without experiencing side effects from the leukocyte apheresis procedure. HCV-RNA became negative within one week in 3 patients (2 were genotype 1b and 1 was 2a), within 2 weeks in 2 patients (1b) and within week 12 in 1 patient (1b). Complete response was obtained in 4 of 6 patients (67%) which is a very impressive efficacy rate compared to IFN plus ribavirin, the other 2 achieved a partial. Response. Additionally, alternative pathway dependent active complement fragments, C3a, C5a and others were found to be high in the post column blood, by up to 10 fold relative to the column inflow.

Conclusions:

The results indicate that granulocyte and monocyte/macrophage adsorptive apheresis might be an effective adjunct to interferon plus ribavirin therapy for eradication of HCV. Further, at present, we have the impression that active complement in the post column blood which perfuses the liver contributes to the clearance of HCV.

Abstract 1223

High Dose Paroxetine and Quetiapine to Augment Interferon and Ribavirin Treatment in Chronic Hepatitis C Patients With Psychiatric Disease

Eric L. Altschuler, Richard E. Kast

Introduction:

Hepatitis C virus (HCV) is the most common viral cause of liver failure in the US. There is no current vaccine and prospects for development of one in the near future seem dim. While it appears that if patients are treated within six months of HCV infection cure rates are greater than 90%, in chronically infected patients and these are the vast majority and testing is not feasible, cure rates with the current best treatment-peginterferon alfa-2a (PEG INF) plus ribavirin (RBV) is only 56% and for the most common viral genotype type 1A only 46%. Given the potential severe neuropsychiatric symptoms from INF, including life threatening depression, psychiatric disease can be a relative, or even absolute, contraindication to HCV treatment.

Results:

We have found that adding high dose paroxetine (Paxil) (40mg BID) and quetiapine (300mg QHS) to INF and RBV has resulted in an excellent HCV cure rate, seven of nine treated patients (eight with type 1A genotype virus), with no suicide attempts or other major psychiatric decompensation. All of the patients had long standing mood disorders and six of the nine had concomitant psychotic illness. None of the patients were HIV+ or HBsAg+. Eight of the nine patients had genotype 1A virus, the other patient had genotype 3A. Eight of the patients had chronic HCV infection and one had more acute disease. Six of the eight patients with genotype 1A cleared the virus, as did the one patient with genotype 3A. Two patients were also taking olanzapine (Zyprexa).

Might these medicines also augment or boost the efficacy of INF + RBV? Indeed, while paroxetine is traditionally considered to be an antidepressant, and quetiapine an antipsychotic medicine these medicines have other pharmacologic properties that could be crucial in fighting HCV: paroxetine is a potent nitric oxide synthase (NOS) inhibitor, and quetiapine is a potent histamine receptor antagonist. (Olanzapine is also a potent histamine receptor antagonist.) As both nitric oxide and histamine are positive trophic factors for HCV, we believe that the paroxetine and quetiapine may augment INF and RBV by antagonizing these factors by lowering systemic or local levels of NOS and inhibiting histamine activity.

Conclusion:

Larger trials of high dose paroxetine and quetiapine to supplement INF and RBV in psychiatric and general patients with chronic HCV infection are warranted.

Abstract 1225

Pilot Study of Interferon Gamma for Chronic Hepatitis C

Alejandro Soza, Theo Heller, Edward Doo, Kittichai Promrat, Glen Lutchman, Lijun Mi, Yoon Park, Harvey Alter, Henry H. Hsu, Marc Ghany, Jake Liang, Jay H. Hoofnagle

Introduction:

There are currently no therapies of proven benefit for patients with chronic hepatitis C who fail to respond to interferon alfa-based therapies. Interferon gamma, a cytokine with no homology to interferon alfa, has marked antiviral effects in vitro in the hepatitis C virus (HCV) replicon system. The aims of this pilot study were to determine the antiviral effects and safety of recombinant interferon gamma-1b in patients with

chronic hepatitis C.

Patient Characteristics:

- ◆ 11 Caucasians; 3 African Americans
- ◆ 9 men; 5 women
- ◆ Mean age 50.4 ± 5 years
- ◆ All genotype 1
- ◆ 6 patients had evidence of advanced fibrosis (ISHAK = 3)
- ◆ All patients had not achieved a sustained response to a previous course of therapy with interferon alfa with or without ribavirin (10 were non-responders and 4 were relapsers).

Methods:

Fourteen patients were randomly assigned to receive interferon gamma in a dose of either 100, 200 or 400 µg sc thrice weekly for 4 weeks. HCV RNA levels were measured 3 times before treatment, then at 6, 12, 18, 24, 48 hours and at 1, 2, 3, 4, 6 and 8 weeks after starting treatment.

Results:

There was no change in HCV RNA titer during therapy; no patient had more than a one log change during the 14 time points). Therapy was associated with significant reductions in neutrophil counts (mean reduction 41%), lymphocyte counts (11%), white blood cell count (28%) and hematocrit (5%). Platelet counts remained unaffected. Similarly, ALT levels were unchanged (mean pre = 80 ± 45 IU/ml, mean at 4 weeks = 72 ± 25 IU/mL, p=NS). There were no differences in response between the high and low dose groups or between previous non-responders and relapsers. Treatment was well tolerated in all patients, with minimal flu-like symptoms and no significant worsening in quality of life scores. No severe adverse events were noted.

Conclusions:

A 4-week course of conventional doses of interferon gamma as monotherapy in patients who had previously failed treatment with interferon alfa had no demonstrable effect on serum aminotransferase levels or HCV viral titer. Whether higher doses, longer duration or combination therapy are effective against HCV remains to be determined.

Abstract 1226

Thrombocytopenia (T) in Patients with Chronic Hepatitis C: Management with Interleukin 11

Charles L. Mendenhall, Abdur R. Shakir, Elizabeth A. Zoiss, Catrina Reese, Hai Bui, Stephen Goldberg, Gary A. Roselle

Introduction:

Of the 4 million people infected with HCV in the US it is estimated that treatment is interrupted or prevented in 1 million due to thrombocytopenia. In many instances this is the result of portal hypertension with secondary platelet pooling and destruction in the spleen. Peripheral platelet antibody destruction may also contribute even in the absence of severe liver injury. Once therapy is initiated the process is further exacerbated by bone marrow suppression associated with interferon therapy (IFN). These combination of events may result in life threatening thrombocytopenia.

Purpose:

Describe thrombocytopenia in the veteran population and indicate one corrective therapeutic action.

Results:

Thrombocytopenia (<120,000) was observed prior to treatment in 25% of 56 patients undergoing therapy for HCV. Therapy consisted of INF alfa 2b + ribavirin (R) (n= 20), Peginterferon alfa PEG IFN 2b (PEG IFN) (n= 12), and PEG IFN 2a (n=10). Platelet changes from baseline(% decrease)at time 2,12,26,48 weeks were - 5.2%,-0.7%,-7.2%,-4.1% on R; -18.9%, -27%, -33.5%, -27.7% on PEG IFN 2b and were -27.4%, -38.1%, -23.4%,(week 48 in progress) on PEG IFN 2a. Of these, 25% needed Interleukin 11 (IL11) to prevent IFN dose reduction or discontinuation and 5% required IL11 prior to IFN to raise platelets to recommended safe IFN treatment levels. All patients responded to IL11. Only side effect observed was fluid accumulation in 5% of subjects, which was easily managed with diuretics.

Conclusion:

Thrombocytopenia is a common problem before and during HCV therapy with IFN. Management with IL11 permits continuation of IFN therapy without dose reduction.

Abstract 1246

Treatment of Acute Hepatitis C Virus with Recombinant Interferon Alpha 2b. Clinical Trial

Enrique R. Arus Sr., Luis Rivera Sr., Mirtha Infante Sr., Marlen Perez Sr., Grisel Soto Sr., Bienvenido Gra Sr., Guillermo Padron Sr., Pedro Lopez Sr.

Aim/Method:

A clinical trial was carried out aimed at evaluating the efficacy and safety of interferon in a group of 13 patients with acute hepatitis C. The diagnosis was made according to biochemical criteria (alanine aminotransferase 2 times the normal value), serological criteria (presence of anti hepatitis virus antibodies), virological criteria (presence of RNA-HCV by PCR) and histological criteria. Treatment with recombinant interferon Alfa 2b 3 000 000 IU was indicated 3 times a week during 12 weeks.

Results:

It was proved that 53.8 % finished the period of treatment with normal alanine aminotransferase and that at the end of follow-up 30.7% had a maintained biochemical and virological response. 4 patients (36.3%) of the 11 that concluded the follow-up had a normal histology in the evolutive hepatic biopsy and of them 2 had a maintained biochemical and virological response, which made us think they were cured.

Interferon was well tolerated and only 38.5% of patients showed secondary manifestations of toxicity. We observed a predominance of cephalalgia (headache), fever, myalgia and arthralgias.

Conclusion:

We concluded that interferon should be used in patients with acute hepatitis C.

Abstract 1256

Biopsy vs. Non-Biopsy: A Comparison of Cost of Treatment of a Biopsy vs. Non Biopsy Model in the Management of HCV Prisoners

Mark J. Marino, William Cassidy, Elizabeth Britton, Nancy Bailey, Anthony Tarver, Monica Prada

Objective:

Analyze cost effectiveness of histologic staging to determine which HCV infected prisoners to treat.

Methods:

HCV infected inmates at Louisiana State Penitentiary are evaluated per a treatment algorithm in which histologic stage determines treatment eligibility. Patients with Stage 0 or Stage 1 fibrosis with a fibrosis index (stage of fibrosis/number of years infected) <0.1 are not treated. Those with Stage 1 with fibrosis index > 0.1 or Stages 2, 3 or 4 (with compensated liver disease) are treated. This cost analysis compares using liver biopsies ("biopsy model") versus treating all patients without contraindications ("non biopsy model"). Patients with at least a 2-log decrease or a negative HCV RNA at week 12 continue treatment for 12 more weeks and if RNA is negative, continue for 24 more weeks. Cost of treating genotype 1 patients with interferon (pegylated and non) an ribavirin was analyzed.

Results:

501 patients were evaluated in the clinic. Liver biopsies were performed on 221 patients. After histological classification, 124 patients were treated with interferon alpha 2b and ribavirin. The actual cost(drug alone) per week of interferon alpha and ribavirin was \$336 and the estimated cost of pegylated interferon and ribavirin(drug alone)was \$397 per week. Cost of treating these 124 patients using the biopsy model was \$15,159 per patient for a total cost of \$1,879,716. In the non-biopsy model, 221 patients would have been treated at a cost of \$12,659 per patient for a total cost of \$2,797,706. A further analysis was performed using pegylated interferon and ribavirin for genotype 1 patients, which revealed a total cost of \$2,082,415 for the biopsy model at \$16,826 per patient treated and \$3,295,739 for the non-biopsy model at \$14,389 per patient treated.

Conclusion:

Management of HCV in the prison system is evolving. A protocol using liver biopsy to establish need for treatment balances cost and complies with current recommendations.

Abstract 1258

The Role of Triple Therapy with Amantadine Sulphate Plus Ribavirin and Interferon-Alpha2a on Chronic Hepatitis C Patients

Ashraf R. Abulfutuh, Mohammed Morsy, Abd El Ghany Solyman, Said El Hendawy, Mohammed El Desouky, Salwa El Hadad, Moemena Kamel

Background:

Controversial reports exist on the usefulness of the application of amantadine as an additional regime in the treatment of patients with chronic hepatitis C.

Methods:

We therefore conducted a study on 400 patients with histologically proven chronic hepatitis C receiving amantadine sulphate (100 mg bid , group 1) or a matched placebo (group 2) together with IFN-alfa 2a induction therapy plus ribavirin (1000-1200 mg/day)for 48 weeks .The two groups showed similar demographic , biochemical and virological baseline characteristics .

Results:

IFN and ribavirin dose reduction was necessary because of side effects in 15% and 16%, and 41% and 33% of the amantadine and placebo group, respectively. Amantadine /placebo dose was reduced in 1% and 5%. Based on intention-to-treat analysis, a sustained virological response after 24 weeks follow-up was observed in 52% of the amantadine group and in 43% of the placebo group ($p=0.055$).The treatment response rate at week 24 was significantly higher in the amantadine group(70%) as compared to the placebo group (59%) ($p=0.02$).Baseline factors significantly associated with sustained response to HCV ($p=0.0001$), GGT ($p=0.001$), ALT ($p=0.008$), age ($p=0.004$), fibrosis stage >2 ($p=0.015$) and body weight ($p=0.05$).

Conclusions:

Triple therapy with amantadine plus IFN-alfa2a induction and ribavirin led to a significant higher on treatment response and also slightly improved sustained virological response rate ($p=0.055$) when compared to combination therapy with interferon alpha-2a induction plus ribavirin. Thus, amantadine seems to have an additional antiviral effect in patients with chronic hepatitis C.

Abstract 1259

Hepatitis A Prevalence in Intravenous Drug Users and Blood Product Infected Hepatitis C Patients.

Fraser Cummings, Shelia O. Cameron, Sharon Hutchinson, Peter R. Mills, John Morris

Introduction:

Some studies of hepatitis A (HAV) superinfection in patients with previous hepatitis B or hepatitis C (HCV) have suggested a poor outcome. In order to develop an anti-HAV vaccination strategy, the number of patients at risk of HAV superinfection needs to be ascertained. No previous studies have looked at the route of HCV infection and the risk of HAV superinfection.

Objective:

The objective of this study was to look at HAV IgG seroprevalence in patients who are at risk of or who already have HCV.

Methods:

IgG anti-HAV were measured in 4 groups: 1) 109 HCV positive IVDU 2) 107 HCV negative IVDU 3) 90 HCV positive patients infected by blood products (BPG) 4) 100 HCV negative blood donors.

Results:

The BPG was significantly older than the other 3 groups. Overall HCV positive patients were more likely to be HAV positive than HCV negative patients (56.3% vs. 36.2% $p<0.01$). There was no significant difference in HAV IgG seroprevalence between HCV positive IVDU and BPG patients. Sub-group analysis demonstrated male HCV positive IVDU were more likely to be HAV positive than the control group or HCV negative IVDU (51.5% vs. 33.3%, $p<0.05$ or 31.9%, $p<0.05$). There were no differences between female groups. Data was also analyzed on the basis of age (<30 or >30). IVDU <30 , regardless of their HCV status,

were more likely to be HAV positive than controls (29.2% vs. 3.7%, $p < 0.001$) but had significantly lower prevalence than those >30 (60.4%, $p < 0.001$). There were no significant differences between patients in the >30 groups.

Discussion:

Our data show that HCV patients are more likely to have been exposed to previous HAV infection; especially if male IVDU. However young IVDU, regardless of HCV status, would be an appropriate group to target for HAV vaccination.

Abstract 1262

Mutagenic effect of ribavirin in NS5A and NS5B regions and response to interferon/ribavirin combination therapy in patients with chronic hepatitis C

Yasuhiro Asahina, Namiki Izumi, Ken Ueda, Kazunari Inoue, Yuki Nishimura, Kaoru Tsuchiya, Kosei Hamano, Jun Itakura, Osamu Noguchi, Masakatsu Uchihara, Shozo Miyake, Nobuyuki Enomoto, Mamoru Watanabe

Background/Aim:

Mechanisms involving antiviral effect of ribavirin against HCV have not been fully elucidated in vivo. To determine the mutagenic effect of ribavirin on clinical response to IFN/ribavirin combination therapy, NS5A and NS5B regions of HCV genome were serially sequenced in chronic hepatitis C patients.

Methods:

Thirty-four patients infected with HCV genotype 1b, which had no or only 1 aminoacid mutation in interferon sensitivity determining region (ISDR), were received 600 to 800 mg of daily oral ribavirin monotherapy for 4 weeks, after which 6MU of IFN and ribavirin combination therapy was given for additional 24 weeks. NS5A including ISDR and NS5B regions were amplified by RT-PCR from sera obtained before and after ribavirin monotherapy, and serial mutations were determined by direct sequencing. Correlation between mutagenic effect and clinical response to subsequent IFN/ribavirin combination therapy was evaluated. Patients in whom HCV RNA could not be detected for 6 months following the termination of IFN/ribavirin therapy were defined as sustained viral responders (SVR). Patients in whom HCV RNA become negative at the end of combination therapy but reappeared were considered as transient responders (TR), and patients who did not become negative were considered to be non responders (NR).

Results:

Sustained viral response was achieved 4 of 34 patients. Remaining 17 patients were TR and 13 were NR. After 4-week ribavirin monotherapy, sequential nucleotide mutations were found at a rate of 1.6×10^{-3} . Nucleotide mutation rate was significantly higher in SVR than TR and NR (5.51×10^{-3} vs. 9.59×10^{-4} and 8.42×10^{-4} , respectively). G to A and C to T mutations were frequently detected at a rate of 1.8×10^{-4} and 3.0×10^{-4} , respectively. Although non-synonymous mutation was rarely found (10%), non-synonymous mutation in NS5A was more frequent in SVR than in TR and NR. Especially, 3 of 5 patients in whom aminoacid mutation in ISDR increased after ribavirin monotherapy achieved sustained viral response. In contrast, only 1 SVR was found in 29 patients who had no increased mutation in ISDR ($p < 0.006$). No significant relation was found between serum ribavirin concentration and a mutation rate.

Conclusion:

Our results suggest that clinical response to IFN/ribavirin combination therapy correlates with mutagenic activity of ribavirin in patients with genotype 1b. Ribavirin may act by promoting IFN sensitive HCV RNA mutation rate in some responders.

Abstract 1267

Significant Percentage of Normal ALT Values seen in Chronic HCV infected patients at a VA Medical Center

Venkat Rangaraj

Background:

HCV is an RNA virus and is the leading cause of liver disease in the United States. It affects about 4 million not including the military personnel. Chronic infection with HCV has been known to lead to cirrhosis in approximately 20% of patients and is an oncogenic virus associated with the development of hepatocellular carcinoma (HCC) in 10% of patients. Acute infection is most often null or asymptomatic hence most cases are not diagnosed at the onset. Of all the HCV infected patients, 85% of these go on to develop chronic infection with approximately 15% undergoing "spontaneous clearance".

Often the diagnosis of HCV infection is confirmed after abnormalities are seen in biochemical tests for liver injury, i.e. ALT (alanine aminotransferase). Serum ALT levels and liver biopsy have been used to assess disease activity. Most, but not all agree that liver biopsy is the more preferable way to determine the degree of liver damage.

In the beginning PCR was too variable between labs and commercially expensive (\$200-\$250 per test) so ALT levels have been the only lab test readily available to follow patients with chronic hepatitis. Some have proposed that a normal ALT indicates minimal or no liver injury. This is difficult to determine in a disease, which is characterized by slow non-linear progression. ALT testing is non-invasive. Normal ALTs are defined as = 50 IU/L and reports range that 26-30% of patients being treated for chronic hepatitis C have normal ALT levels. ALT levels alone are not an adequate way to assess progression.

Aim:

This study was undertaken to further clarify the significance of normal ALT in veterans with active chronic HCV infection.

Methods:

Eighty seven HCV positive outpatients referred for treatment at the VA Medical Center Cincinnati were studied prospectively. Pre-treatment laboratory tests included ALT levels, viral genotypes and HCV-RNA loads were obtained on every patient. Patients with established disease were treated with interferon alpha 2b or Pegylated interferon alpha 2b in combination with Ribavirin using generally accepted protocols. Serum HCV-RNA levels were obtained at 0, 3, 6, 12 months after initiating treatment and again at 18 months (6 months post treatment). Pre-treatment liver biopsy to stage the fibrosis was performed on every patient. Treatment was not initiated on any patient if consumption of alcohol was observed in the preceding 3 month period. We then compared the following 7 variables (race, age, virology genotype, nutrition, biopsy result and response to treatment) of each of the two clinical groups, (normal vs elevated ALT levels).

Results:

From a pool of 87 patients (85 males, 2 females), we identified 29 patients (33.33%) with normal serum ALT (<50 IU/L) and 58 patients (66.67%) with >50 IU/L serum ALT at baseline. On liver biopsy, 9 of the 29

patients (34.48%) with normal ALT had cirrhosis or incomplete cirrhosis. (stage 2.5 to stage 4). In patients with elevated ALT, the prevalence of cirrhosis/incomplete cirrhosis was seen in 50% of the population. Differences in histological injury seen on liver biopsy ($p < 0.09$) and nutritional status (BMI) ($p < 0.08$) showed a trend towards significance ($p > 0.05 < 0.10$). We noticed no significant differences in race, age, virology, or response to therapy. ($p > 0.05$). Fisher exact test was used to compare the characteristic data. Linear regression analysis however showed a significant ($p = 0.05$) linear relationship between ALT and liver fibrosis on biopsies.

Discussion:

At baseline just prior to the initiation of treatment with IFN alpha 2a and RBV, normal ALT serum level (0-50 IU/L) was observed in 33.33% (29/87) of the subjects. If one examines past records for results of prior ALT test of liver injury over a six month period the % of persistently normal ALT values is reduced to 21-25%. This is comparable to that previously reported. Using the VA computerized data retrieval system (CPRS), ALT levels measured prior to baseline could be easily retrieved back 10 years.

One contributing factor for the high incidence of normal ALTs may be a high occurrence of alcoholism. In our population prior alcohol abuse was recorded in over 90%> It has long been recognized that both ALT and AST are lower in alcoholic liver disease than might be anticipated particularly with evidence of alcoholic liver present. This is especially true of the ALT so that the ration of AST:ALT becomes elevated. Indeed a ration value of >2 has been used for diagnosis purposes to differentiate alcoholic verses viral etiologies.

It is noteworthy that all our patients were required to exhibit sobriety for at least 3 months prior to treatment. Whether 3 months sufficient time to lose the alcohol effect is remains to be established. The more important question is the clinical significance of normal ALT at baseline.

Our studies indicate that a normal ALT did not preclude more severe liver injury since 34.48% (9/29) of our normal ALT patients had cirrhosis or incomplete cirrhosis which would have been unrecognized in the absence of histological conformation. None the less, the ALT relationship to liver pathology showed the best correlation.

Patients with elevated ALTs had the higher prevalence of cirrhosis/incomplete cirrhosis seen in 50%. Regression analysis confirmed this relationship showing a significant linear correlation between ALT levels and the range of pathology (stages 1 to 4) $p < 0.05$. None of the other 6 variables analyzed showed a significant relationship ($p > 0.05$)

Conclusion:

Our studies indicate that a normal ALT (0-50 IU/L) did not preclude more severe liver injury in a significant percent of cases. Therefore, the use of ALT in patients with HCV infection is not a predictable indicator of significant underlying liver disease.

Abstract 1269

Steatosis as a Predictive Factor for Treatment Response in Patients with Chronic Hepatitis C

Ivan Antunez, Nestor Aponte, Alberto Fernandez, Doris H. Toro, Federico Rodriguez-Perez

Background:

Hepatic steatosis has been described in 31-72% of chronic hepatitis C (HCV) liver biopsies. It has been related to disease progression and suggested as a predictor of treatment response in chronic HCV.

Aim:

This study aims to evaluate the presence and degree of steatosis in liver histology of patients with chronic HCV prior to combination therapy with interferon (INF) and ribavirin (RBV), and how it influences treatment response.

Methods:

The hospital records of patients with chronic HCV who received treatment at the San Juan VA Medical Center from 1998 to 2002 were reviewed. All patients completed therapy, had a pre-treatment liver biopsy, genotype determination, and pre & post treatment HCV-RNA levels. Patient's age, sex and body mass index (BMI) were examined. Pre-treatment liver biopsy slides were reviewed and graded for steatosis by a double-blinded hepatopathologist. Steatosis was graded by the presence of fat in total biopsy area as: mild (<33%), moderate (33-66%), severe (>66%) or absent. Treatment response was defined as virological clearance measured by HCV RNA at the end of treatment and 24 weeks after completion of treatment. The presence of steatosis was compared to BMI, HCV genotype and treatment response.

Results:

46 records met the inclusion criteria. All patients were male of Hispanic origin. Mean age: 52.2 years (range: 40-68). Mean BMI: 27.5 kg/m² (range: 21.1-35.9). HCV genotype 1 was equally distributed in all groups with an overall prevalence of 75%. 82.6% (38/46) of the patients had hepatic steatosis: 29 (63%) mild, 7 (15%) moderate and 2(4%) severe. 16.6% (8/46) of the biopsies did not show steatosis. Overall, the response rate for those with steatosis was 31.6% (12/38) : 10/29(34.5) mild, 1/7 (14.3%) moderate and 1/2(50%) of severe. 75% (6/8) of those without steatosis responded to treatment. This difference (31.6% vs.75%) was statistically significant (p=.042). The mean BMI of both groups was similar (27.7 kg/m² steatosis and 26.6 kg/m² no steatosis). This difference was not statistically significant (p=.308).

Conclusion:

The results of our study show a high prevalence of steatosis in the liver histology of patients with chronic HCV. The presence and degree of steatosis in our HCV patients appears to be unrelated to either genotype or BMI. Furthermore, the response to therapy is negatively influenced by the presence of steatosis regardless of genotype. Hepatic steatosis, either mild, moderate or severe, appears to be an independent predictor of poor response to therapy.

Abstract 1272

Nonlinear HCV and linear ALT Dynamics in serum during high dose Interferon

Gerond Lake-Bakaar, Lynda Ruffini, Simon Frost

Background:

Current mathematical models that describe serum HCV dynamics during therapy with interferon fit experimental data using monotonic biphasic decay curves similar to those described by Neumann et al 1998 (Science 282:103-7). Although these models fit the data well during the first 48 hours of therapy (phase 1), they fail to fit data obtained over next several days (phase 2). A possible constraint of the bi-experimental model is the assumption that viral decay or growth rates remain constant. Several factors such as drug selection pressure, changes in target cell population (predator-prey) interaction, pharmacokinetics and host immunity all serve to alter the virus characteristics and could account for the marked variability observed in phase 2.

Aim:

The aim of this study is to analyze HCV RNA changes in sera during daily high dose IFN alpha 2a ± RBV ± Amantadine using generalized non-linear least squares and functional data analysis.

Methods:

We modeled nonlinear dynamics using cubic splines, which allow a wide range of curves to be fitted. These models are equivalent to assuming that at any one time, the log viral load (or log ALT) changes linearly over time, equivalent to exponential decay or growth, and that the decay or growth rate, $r(t)$, changes over time according to a random walk, and include linear dynamics as a special case. We fitted these models to the dynamics of HCV and ALT in 16 patients with chronic HCV liver disease. Eight patients received I monotherapy, 10 mIU daily and eight received combination therapy with I and ribavirin, R, 1000 mg daily or I + R and Amantadine, 200 mg daily. Paired HCV RNA and ALT measurements were taken at frequent (2-24 h) intervals over 14 days. The decrease in viral load over the first 24 hours of therapy was used as a surrogate for treatment efficacy. Patients grouped by response:

- ◆ Monotherapy $n=8$ – Rebound $n=4$ (Group 1) and
- ◆ non-rebound $n=4$ (Group 2)
- ◆ Combination therapy $n=8$ - IFN + RBV 1000mg $n=5$ (Group 3) and
- ◆ IFN +RBV+ Amantadine $n=3$ (Group 4)

Results:

Log ALT dynamics were close to linear over the 14 days. In 4 of 8 patients on monotherapy (group 1), serum ALT levels rose (doubling time 9-32 h), whereas in the remaining 4 (group 2) and in all combination therapy patients (group 3), ALT levels fell with half-lives of 10-48 h and 9-64 h respectively. Viral dynamics in these patients were highly nonlinear.

- ◆ Group 1 exhibited sustained increases in both ALT and viral load after 48 h of therapy, while groups 2 and 3 exhibited a trend of decreasing ALT and viral loads, with some patients exhibiting transient HCV increases. While there was a strong negative correlation between efficacy and baseline viral load, ($r=0.89$), there was no correlation between the viral load decrease and the rate of ALT change ($r=-0.26$), particularly when group 1 was excluded ($r=0.09$).
- ◆ Less tendency to exhibit rebound in the 1st 7 days of therapy in patients on dual and triple therapy compared to monotherapy
- ◆ Relative to mono, dual and triple therapy had no effect on the initial rate of viral decay

Conclusion:

Although peak viral load in group 1 was similar to or less than baseline, ALT levels rose steadily, suggesting a possible hepatitis flare with a new more cytopathic and interferon resistant viral variant. The lack of correlation between ALT and HCV decay suggests a more complex quantitative relationship between phase 2 HCV decay and hepatocyte death (ALT dynamics) than has been suggested by current models. HCV RNA changes in serum can be analyzed using generalized non-linear least squares and functional data analysis and appears to more closely mirror the observed data compared to the bi-experimental model.

Abstract T1274

The Potential to Increase the Number of Hepatitis C Patients Receiving Treatment.

Introduction:

In order to predict the financial implications of Hepatitis C (HCV), the National Institute of Clinical Excellence (NICE) estimates 12.5% of those detected will receive treatment. At present data is limited on the potential to reduce the gap between individuals diagnosed and those commencing therapy.

Methods:

HCV ELISA positive patients in Northern Ireland (NI), prior to confirmation by Recombinant Immunoblot Assay, were identified from laboratory records and clinical data was sought.

Results:

Of 692 HCV ELISA positive patients, 556 (80.3%) had hospital charts; 403 charts were available for review. 189 patients (46.9%) had attended dedicated a HCV clinic, of which 156 were PCR positive. 106 of these patients underwent liver biopsy, and in 54 cases treatment was indicated.

Treatment has been commenced/is pending in 36 (33.9% of total). No adequate clinical reasons were identified in 22 of those not biopsied and in 9 of those failing to undergo treatment.

Conclusion:

Uptake of HCV therapy in Northern Ireland (8.9%) is below that predicted by NICE (12.5%). Although 80.3% of HCV patients have attended a North Ireland hospital for initial/further HCV testing, only 46.9% have attended an HCV clinic.

Increasing HCV awareness amongst hospital doctors could potentially double the number of patients presenting for assessment. More effective patient counseling to minimize patients dropping out could increase liver biopsy uptake from 56.1% of those attending the clinic to 82.1%, and increase the uptake of treatment from 33.9% to 42.5%. Thus increases in doctors' education and patient counseling could produce a dramatic increase in the number of patients receiving treatment.

Abstract 1275

Predictive factors for dose modification and premature discontinuation of interferon plus ribavirin for adverse effects in Japanese patients with chronic hepatitis C

Yoshiaki Iwasaki, Yasuyuki Araki, Hiroshi Ikeda, Masaharu Ando, Keiji Kita, Koh-Ichi Takaguchi, Tomonori Senoh, Haruhiko Kobashi, Kazuhisa Yabushita, Masaki Ohmoto, Toshiya Osawa, Mitsuhiko Kawaguchi, Toshinari Shimoe, Jun-Nosuke Shimamura, Shin-Ichi Fujioka, Kohsaku Sakaguchi, Hiroyuki Shimomura, Yasushi Shiratori

Background:

Interferon-a plus ribavirin therapy for chronic hepatitis C is associated with adverse effects that lead to dose modification or premature discontinuation of therapy in up to 27% of patients in randomized controlled trials.

Aim:

The aim of this study was to examine the predictive factors for dose reduction or therapy discontinuation in Japanese patients with chronic hepatitis C treated with combination therapy in current clinical practice.

Methods:

We prospectively enrolled 128 consecutive Japanese patients with genotype 1b chronic hepatitis C. They were scheduled to receive 6 or 10 million units of interferon- α 2b daily for two weeks and then three times per week for another 22 weeks and 600 or 800 mg of ribavirin per day throughout the therapy. Patients were regularly assessed for safety and tolerance by monitoring adverse events including laboratory abnormalities. Dose modification and premature discontinuation of the combination therapy due to adverse events or laboratory abnormalities were the endpoints.

Results:

Dose reduction or discontinuation of ribavirin were required in 25 of 128 (19.5%) patients. Dose reduction of interferon- α 2b or discontinuation of therapy were required in 17 of 128 (13.3%) patients. Accordingly, 42 patients (32.8%) failed to complete the combination therapy due to adverse events. Logistic regression analysis revealed that age (>55 years) and gender of patients were significantly associated with the dose reduction or discontinuation of ribavirin ($p=0.027$; Odds ratio=1.058; 95% CI, 1.006-1.112, and $p=0.038$; Odds ratio=0.421; 95% CI, 0.186-0.951 for age and male gender, respectively).

Previous interferon therapy was the factor that was associated with resistance to discontinuation of the combination therapy ($p=0.011$, Odds ratio=0.067, 95% CI; 0.008-0.531). Failure to complete the combination therapy was significantly associated with female gender ($p=0.016$, Odds ratio=2.54, 95% CI; 0.184-0.843).

Conclusions:

Our data demonstrated that dose modification and discontinuation of therapy were more frequent in Japanese patients treated in current clinical practice than in those treated in the USA. Age of patients (>55 years), female gender, and naive patients were associated with dose modification or discontinuation of therapy. Thus treatment schedule should be modified among these patients to reach high efficacy by the rules of 80%, 80%, and 80%.

Abstract 1278

African Americans Failing Treatment with Interferon Monotherapy for Chronic Hepatitis C Are Less Likely to Achieve Sustained Response to Subsequent Retreatments Compared to Caucasians.

Irena Zalewska, Firdous Siddiqui, Murray Ehrinpreis, Ravi Dhar, Ravindra Murthy, Lenore Ranieri, James Janisse, Milton Mutchnick

Background:

African Americans are less likely to respond to interferon (IFN)-based therapies than Caucasians.

Aim:

To determine and compare the sustained virological response (SR) rates in African Americans and Caucasians who received 3 courses of IFN-based therapy for chronic hepatitis C (CHC). Sustained virological response was defined as undetectable HCV RNA 6 months after the end-of- treatment.

Methodology:

This was a retrospective study. Patients who received IFN monotherapy and those who were subsequently

treated with one or two courses of combination therapy were identified. The SR rate was determined for each consecutive treatment and the results were compared between African Americans and Caucasians. Variables affecting treatment outcome, such as genotype and 12-week HCV RNA levels, when available, were analyzed.

Results:

1. 234 patients (African Americans=140; Caucasians =94) received IFN monotherapy. Race was a significant predictor of SR to monotherapy in patients who completed this treatment, 7 (5%) African Americans, 9 (10%) Caucasians ($p<0.001$). Genotype was available for 117 African Americans (type 1=106; type non-1=11) and for 79 Caucasians (type 1=61; non-1=18). Only 1 (1%) African American with type 1 had a SR compared with 5 (45%) African Americans with non-1 ($p<0.001$). Genotype was not a predictor of SR in Caucasians ($p=0.11$).
2. One hundred patients (African Americans =58; Caucasians =42) received a second treatment with a combination of IFN alpha-2b and modified weight-based ribavirin. Race again was a significant predictor of SR, 6 (10%) African Americans, 18 (43%) Caucasians ($p<0.0001$). Genotype was available for 43 African Americans (type 1=40; non-1=3) and for 36 Caucasians (type 1=29; non-1=7). Genotype was a predictor of SR in both African Americans and Caucasians. Three (8%) African Americans with genotype 1 and 3(100%) African Americans with non-1 genotype had a SR ($p<0.004$). Nine (33%) Caucasians with genotype 1 and 6 (86%) with non-1 genotype had a SR ($p<0.04$). Negative PCR for HCV RNA at 12 weeks of treatment was a significant predictor of SR in both African Americans and Caucasians. All African Americans and Caucasians who achieved SR had undetectable levels of HCV RNA at 12 weeks.
3. Twenty six patients (18 African Americans and 8 Caucasians) received a third course of treatment with pegylated-IFN (PEG-IFN) alpha-2b and ribavirin of varying dose and schedule. Only 1 Caucasian achieved SR, 2 patients (1 African American, 1 Caucasian) had an end-of- treatment response, SR results are pending.

Discussion:

- ◆ Our analysis which includes one of the largest groups of African Americans revealed that African Americans have a significantly decreased rate of SR to all IFN-based therapies compared with Caucasians. This report is consistent with previous reports.
- ◆ We also demonstrated that non responders (African Americans and Caucasians) to monotherapy achieved only modestly higher rates of SR when retreated with combination therapy.
- ◆ More importantly, our study showed that retreatment of non-responders to combo therapy results in a limited benefit to both groups.
- ◆ HCV genotype is a major predictor of SVR. However, it may play a more important role in African Americans as they are more frequently infected with HCV genotype 1.
- ◆ More clinical trials as well as evaluation of more aggressive treatment protocols in chronic hepatitis C are required that will include a significant number of African Americans.

Conclusion:

African Americans have a significantly lower rate of SR to all IFN-based therapies than Caucasians. Although combination therapy with IFN alpha-2b and ribavirin modestly improves SR rate, retreatment with PEG-IFN and ribavirin of African Americans failing combination therapy does not appear to be effective.

Abstract 1279

A combined therapy with high dose of interferon (IFN)-alpha as an induction and ribavirin in non-responders to IFN alone with chronic hepatitis C

Background and Aim:

A combined therapy with IFN-alpha and ribavirin has been reported to increase the response rate in patients with chronic hepatitis C (CH-C). The antiviral mechanisms of this therapy for CH-C, however, still remain poorly understood. Here we have attempted to examine the efficacy of an induction therapy with high dose of interferon (IFN)-alpha and ribavirin from the view point of Th1/Th2 balance.

Methods:

Thirty nine chronic hepatitis C patients (30 males, 9 females) with genotype 1b and high load of HCV-RNA who did not respond to an IFN monotherapy, were treated with 10 MIU of IFN-alpha2b and 800 mg of ribavirin a day as an induction therapy for 2 weeks. Thereafter, 6 MIU of IFN-alpha2b (3 times /week) and the same dose of ribavirin were administered for up to 24 weeks. Serum HCV-RNA levels were investigated by Amplicor method. Using peripheral blood lymphocytes, minus-strand of HCV-RNA was detected by RT-PCR. Th1/Th2 balance was analyzed by two color flowcytometry using IFN-gamma and IL-4 monoclonal antibodies, respectively. Serum ribavirin concentration was measured by HPLC. Complete response, defined as the disappearance of HCV-RNA was determined at 24 weeks. These data were compared before treatment and at 4, 24 W between complete responders (CR) and non-responders (NR).

Results:

The response rate at 24 W in this treatment was 76.9 %. The mean duration until the disappearance of HCV-RNA was 5.4 W. The disappearance of minus-strand of HCV-RNA in peripheral blood lymphocytes was consistent with that of HCV-RNA in serum. Th1/Th2 ratio was elevated by 6.6plus minus 6.5 % at 4 W and 25.1plus minus17.7 % at 24 W in CR, while it was not changed at 4W (- 4.3 plus minus14.7 %) and 24W (0.3 plus minus12.3 %) in NR. There were no significant differences of ribavirin concentration between CR and NR (2.5plus minus0.2 VS 2.3plus minus0.4 at 4W, 2.2plus minus 0.2 VS 1.8plus minus0.6 mg/ml at 24W). A percent decrease in Hb was 22.2 plus minus2.3 % in CR and 15.9puls minus 2.1 % in NR at 24W.

Conclusions:

Our combined therapy with high dose of interferon (IFN)-alpha as an induction and ribavirin for non-responders to IFN monotherapy showed a high response rate in people with chronic hepatitis C. It is speculated that the efficacy may be mediated by Th1/Th2 balance, but not by ribavirin concentration.

Abstract 1280

Triple Combination of Pegylated Interferon Alpha 2b, Ribavirin and Amantadine for Treatment of Chronic Hepatitis C

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

Background:

Addition of amantadine (AMANT) to pegylated interferon alpha 2-b (PEG-IFN) and ribavirin (RIBA) may enhance efficacy of this anti-viral regimen for chronic hepatitis C.

Aim:

In a multi-center clinical trial, the safety and efficacy of this triple combination regimen were assessed.

Design:

Patients with chronic hepatitis C {elevated ALT, HCV RNA (+) by PCR} were enrolled {67 treatment naive and 101 without previous sustained virologic response (SVR)}. Patients were started on PEG-IFN at a dose of 1.5 mcg/kg weekly with 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. Intention-to-treat analysis is being reported.

Results:

Of 168 patients enrolled, 74% were male, age 47.26±5.73, BMI 28.87±5.02, 79.2% were white, 84% had genotype 1 and 4, 16% genotype 2 and 3, and 36% with cirrhosis. Their baseline HCV RNA was 689,242±698,030 IU/mL with a baseline ALT of 107.25±79.09.

- ◆ Of the entire cohort, 35 (21%) discontinued early due to side effects or loss to follow up. Significant anemia (hemoglobin<10 g/dL) occurred in 19% (32/168) while severe anemia (hemoglobin<8.5 g/dL) occurred in 0.6% (1/168).
- ◆ For the entire cohort, early virologic response after 24 weeks of therapy (ER) was 40.5%, with an end-of-treatment virologic response (ETR) of 35.7% and a SVR of 25%. This response was higher in patients who were treatment naive than those who were non-responders to previous treatment (ER 53.7% vs. 32.7%, p=0.001, ETR 47.8% vs. 28.6%, p=0.04 and SVR 34.3% vs. 19.4%, p=0.01). Additionally, those with genotype 1 and 4 had lower response rates than those with genotype 2 and 3 (ER: 36% vs. 69%, p=0.004, ETR: 32% vs. 58%, p=0.005 and SVR: 21% vs. 46%, p=0.001).
- ◆ Patients with advanced fibrosis (METAVIR stage 3 and 4) had lower response rates than those with minimal or mild fibrosis (METAVIR stage 0-2) (ER: 25% vs. 47%, p=0.057, ETR: 17% vs. 41%, p=0.024 and SVR: 10% vs. 30%, p=0.087).
- ◆ African-American patients had lower response rates than Caucasians or other ethnic groups (ER: 21% vs. 49% vs. 20%, p=0.01, ETR: 13% vs. 41% vs. 20%, p=0.086, SVR: 4% vs. 29% vs. 20%, p=0.039). BMI, gender and age did not affect SVR.

Conclusion:

The addition of amantadine to PEG-IFN and RIBA does not increase the efficacy of this anti-viral regimen

Abstract 1283

Treatment of HCV-Related Mixed Cryoglobulinemia with Interferon and Ribavirin

John M. Levey, Edie McNamara

Purpose:

Mixed cryoglobulinemia(MC)is a systemic vascular disease characterized by palpable purpura, arthralgias, and fatigue. The pathogenesis of MC involves the presence of serum immunoglobulins, which reversibly precipitate upon cooling. Type II MC is most closely associated with chronic hepatitis C (HCV) infection. About 80% of cases of MC are caused by HCV infection. We sought to determine the sustained viral response rates(SVR) in HCV patients with, and without MC after treatment with interferon 2b(IFN) and ribavirin. In addition, we determined if patients cleared their MC after treatment.

Methods:

We reviewed treatment records of 41 consecutive patients who had a complete course of combination therapy (24 weeks in genotype non-1, 48 weeks in genotype 1). Qualitative serum cryoglobulins were drawn prior to treatment and handled per lab protocol. Patients received IFN 3 million units thrice weekly and ribavirin 800-1200 mg./day. Patients who required major dose adjustments were not included in the study. SVR and clearance of MC were determined six months post-treatment.

Results:

Total rate of SVR was 43.9% (18/41). SVR in genotype 1 patients was 25.0% (7/28). SVR in genotype non-1 patients was 84.6% (11/13). Incidence of MC was 17.1% (7/41). In all MC patients, clearance of MC post-treatment was 85.7% (6/7). Clearance of MC in genotype 1 patients was 75% (3/4). Clearance of MC in genotype non-1 patients was 100% (3/3). No patients cleared MC without a SVR. The one patient who did not clear MC was genotype 1.

Conclusion:

HCV-related MC can readily be cleared with IFN/ribavirin treatment. This seems contingent on SVR. In this small study group, there was an indication that the MC group had a higher rate of SVR. Similar to the HCV population as a whole, this appeared especially likely in genotype non-1 patients.

Abstract 1284

Study of Hepatitis A Virus Superinfection to Hepatitis C Patients

Ashraf R. Abulfutuh, Mohammed Morsy, Abd El Ghany Solyman, Said El Hendawy, Mohammed El Desouky, Salwa El Hadad, Moemena Kamel

Background:

The significance of super-infection with the hepatitis A virus (HAV) in patients with chronic hepatitis C had been a matter of debate. While some studies suggested an incidence of fulminant hepatitis of up to 35%, no significant effect of HAV on HCV was reported by others. The aim of this study was to investigate the effect of HAV super-infection on HCV replication in 170 anti-HCV-positive patients between 1995 and 2002. Anti-HAV-IgG- and anti-HAV-IgM-testing was performed.

Results:

Eleven anti-HCV-positive individuals with acute HAV super-infection were identified. Importantly, none of the patients had a fulminant course of hepatitis. Overall, HCV-RNA was detected by PCR in 81% of the anti-HCV+ patients. In contrast, HCV-RNA was present in only 3 of the 11 anti-HCV-positive patients with acute hepatitis A (29%), indicating suppression of HCV replication by HAV superinfection ($p < 0.0001$). No effect of previous HAV infection on HCV replication was evident (81.9% HCV-RNA+ vs. 81.3% HCV-RNA+ for anti-HAV-IgG-positive and anti-HAV-IgG-negative patients, respectively). Serial follow-up samples were available in 3 of the acute cases. After recovery from hepatitis A, HCV replication increased again in 2 individuals while one patient remained HCV-RNA-negative after clearance of HAV throughout follow-up.

Conclusions:

HAV super-infection is associated with decreased HCV-RNA replication which may lead to recovery from HCV in some individuals. Fulminant hepatitis A is a rare event in patients with chronic hepatitis C.

Abstract 1285

Incidence of High Depressive Symptoms in Chronic Hepatitis C (CHC) Patients Following Interferon Plus Ribavirin Therapy.

Dhiman Basu, Cinda H. Clark

Background:

Depression, fatigue and functional disability are being reported in patients with chronic hepatitis C naïve to treatment. In monotherapy with interferon alpha used for the treatment of chronic hepatitis C is known to induce an inter-correlated stimulation of cytokine network and an increase in depressive symptoms as well. It is also known that functional disability seen in chronic hepatitis C patients is being contributed more often by the depressive symptoms than by the hepatic disease itself and can increase the incidence of non-compliance leading to treatment failure.

Purpose:

The purpose of this study is to assess whether interferon (INF) plus ribavirin (RBV) therapy has an impact on the incidence of high depressive symptoms in chronic hepatitis C (CHC) population and whether such changes vary amongst different ethnic groups.

Methods:

Secondary analysis of data collected from a previous study was used to evaluate the incidence of depressive symptoms. The Center for Epidemiologic Study of Depression (CES-D), a self-report 20-item 4-point likert scale (scores range 0-60) with good reliability ($\alpha = 0.91$) and an established construct validity in the CHC population, was used. Sample included non-cirrhotic CHC subjects with compensated liver disease at three outpatient facilities in a metropolitan area with no or limited depressive symptoms (CES-D scores < 25), no other psychiatric issues, currently not taking antidepressants and English speaking. CES-D questionnaires used were those previously collected prior to and at the end of 24 weeks of INF+RBV therapy. Data were analyzed using MINITAB 12.

Results:

Of the initial 294 evaluated, 69 subjects were used in this analysis. There were 34 Caucasians, 19 African-Americans, 11 Hispanics and 5 Vietnamese Asians. Mean CES-D scores prior to INF+RBV and at the end 24 weeks of therapy for all subjects combined were 11.93 ± 7.61 and 19.21 ± 12.30 respectively, with a significant difference identified ($p = 0.029$ by ANOVA). There were 19 subjects with new onset of high depressive symptoms (CES = D = 25) at the end of 24 weeks of therapy. Overall incidence of high depressive symptoms following INF + RBV therapy in CHC patients was estimated to be 26%. Mean CES-D scores pre-therapy; mean CES-D scores end of 24 weeks of therapy were 12.91 ± 7.36 ; 22.32 ± 11.84 for the Caucasians, 14.05 ± 7.63 ; 18.95 ± 12.67 for the African-Americans and 11.46 ± 7.50 ; 17.91 ± 13.23 for the Hispanics and 9 ± 6.86 ; 15.8 ± 10.67 for the Vietnamese Asians respectively. CES-D scores for the Caucasians were significantly higher at the end of 24 weeks of therapy compared to pre-therapy [$p < 0.01$ and CI (-13.31, -5.51) by paired t test]. But there were no significant differences in the CES-D scores amongst African-Americans and Hispanics prior to and at the end of 24 weeks of therapy.

Conclusions:

Incidence of high depressive symptoms amongst patients with CHC treated with INF + RBV in our study was 26%, as compared to the approximately 5-45% reported in various clinical trials. Caucasians had higher incidence of depressive symptoms following INF + RBV therapy compared to African-Americans, Hispanics

or Vietnamese Asians.

Abstract 1286

Differential Response Rates to Clearance of Hepatitis C Virus in Chronic Hepatitis C, Based on Racial Makeup of Patients Treated With Interferon/Ribavirin (I/R) or Peg/Ribavirin (Peg/R) Combination

Barry J. Levitt, Ahmed D. Abdalrhim, Nagi H. Ahmed, Vinod K. Thangada, Aslam Malik, Victor Fishman, Mathew Bromer, Michael Mlecko, Radhika Srinivasan, Martin Black, Larry S. Miller

Background:

We have noticed that Afro-American patients treated with Interferon/Ribavirin or PEG/Ribavirin combination therapy seem to have sustained clearance of Hepatitis C virus at a lower rate than Caucasian patients in our practice.

Purpose:

To determine the viral clearance rate of Hepatitis C virus in patients with chronic Hepatitis C treated with Interferon/Ribavirin or PEG/Ribavirin combination based on racial makeup.

Methods:

This is a retrospective review of 287 patients with documented Hepatitis C (PCR positive) who were treated with Interferon/Ribavirin or PEG/Ribavirin combination therapy. There were 170 Caucasians, 32 Hispanic and 85 Afro-American patients. The percentage of patients with sustained clearance of the virus for six months post-treatment was calculated for each racial group.

Results:

7% of Afro-American patients cleared the virus. 28% of Hispanic patients cleared the virus. 42% of Caucasian patients cleared the virus. The difference in clearance rates of the virus between Afro-Americans and Caucasians was highly significant with the $p < 0.0001$. The difference in clearance rates between Caucasians and Hispanics was significant with $p < 0.04$. The difference in clearance rates between Afro-Americans and Hispanics was significant with $p < 0.02$.

Conclusion:

Afro-American patients with Chronic Hepatitis C showed a significantly lower sustained clearance rate to Interferon/Ribavirin or PEG/Ribavirin combination therapy than Caucasian or Hispanic patients.

Abstract 1287

Efficacy of Hepatitis C treatment is a function of ethnicity

Duke D. H. Nguyen Md, Dhiman Basu Md, Cinda Clark Rn Dsn, Gene Lesage Md

Purpose:

While sustained virologic response to non-pegylated interferon a-2b (INF) and ribavirin (RBV) is well established, the response to treatment in non-Caucasians, in particular Hispanic and Vietnamese are poorly documented.

Aim:

Our aim was to compare the response rate at two publicly funded and one tertiary referral center in a multicultural city.

Method:

Data was obtained from those who underwent treatment with INF + RBV at the aforementioned centers between June 1998 and June 2002. Those who underwent treatment were categorized as achieved sustained response (i.e. negative viral load 6 months post-treatment) and those that were not. These two groups were further studied, looking at variables associated with site (tertiary referral/publicly funded centers), gender (M/F), age groups (<40/>40), ethnicity (Caucasian/ African American / Hispanic/ Vietnamese).

Results:

- ◆ A total of 289 patients were evaluated.
- ◆ There was no statistically significant difference in response between the tertiary center and the publicly funded centers (37/96, 39% vs. 59/192, 31% respectively; $p = 0.185$), or between male and female (46/150, 31 % vs. 50/139, 36% respectively, $p = 0.339$).
- ◆ There was a statistically significant higher response rate in patients younger than 40 years of age (18/37, 49% vs. 78/243, 32%, $p < 0.05$); and higher response rate in Vietnamese 17/25, 68% than Caucasian 55/129, 43%, Hispanic 14/42, 33%, and African American 10/93, 11 %; $p < 0.001$.
- ◆ Compared with the Caucasian patients, the odds ratio of Vietnamese sustaining a response was 2.86 (95% C.I. 1.15-7.10), Hispanic 0.67 (95% C.I. 0.32- 1.40) and African American 0.16 (95% C.I. 0.08-0.34) ($p < 0.001$)

Conclusion:

The ethnic background of the patient strongly influences response rate, which favored Vietnamese over Caucasian, Hispanic and African American in descending order. Patients less than 40 years of age have better response rate. The results above provide novel information on response rate for the previously unstudied ethnic groups (Hispanic and Vietnamese). Hence, the impact of ethnicity on response to treatment is important and should be considered.

Abstract 1289

Patient's Misconceptions Regarding The Hepatiitis C Virus Before And After An Educational Class

Ruth Corbett, Karen K. Luken, Terri Finnigan, Allan P. Weston, Daniela Mitreva

Background:

When patients first present to the practitioner, often an assumption is made about the patient's basic level of understanding about the Hepatitis C virus. A treatment plan is sometimes prescribed without assessing the patient's level of knowledge. Basic education is key to patient understanding, resulting in increased adherence to the treatment plan and promotion of a healthy lifestyle. A group educational setting is an avenue to provide necessary basic Hepatitis C education in an efficient and effective manner.

Purpose:

The purpose of this research was to evaluate the patient's basic level of understanding about Hepatitis C virus when walking into the provider's office. The second purpose was to determine if the patient's level of understanding improved after a group Hepatitis C educational class.

Methods:

Patients diagnosed with Hepatitis C were referred by their Primary Care provider for consultation. These patients were scheduled into a group educational clinic for evaluation of knowledge and basic education of their disease process before seeing the specialist. An hour-long didactic session regarding transmission, treatment, and prevention was presented with opportunity for questions. An 18-point test was administered before and after the educational class. The test examined risk factor identification, ETOH and interferon effects on the liver, vaccination necessity and preventative measures.

Results:

A total of 43 patients from the Kansas City VA Medical Center were given a 5-question pre and posttest covering transmission, prevention and treatment. The pre test scores averaged 67% with SD +/- 17.4. Post-test scores averaged 87% with SD +/- 13.07, which is statistically significant (p.0.0001). An alarming misconception among these veterans is that intranasal cocaine use was not recognized as a risk factor for Hepatitis C transmission in 72% of the patients.

Conclusions:

Considerable amount of misconception about Hepatitis C transmission, prevention and treatment is present in the veteran population. This study shows vast improvement in education scores after a one-hour didactic education class. Further follow up is necessary to see if increased education can lead to increased adherence and improved healthy lifestyle.

Abstract 1292

PEG-Interferon a-2b + Ribavirin for Treatment of Patients with Chronic Hepatitis C Who Have Previously Failed to Achieve a Sustained Virologic Response Following Interferon alfa or Interferon a-2b + Ribavirin Therapy.

Mark Sulkowski, Ken Rothstein, Lawrence Stein, Elliot Godofsky, Russell Goodman, Douglas Dieterich

Background:

The role of Pegylated interferon(IFN) alpha-2b (PEG) and ribavirin (RBV) therapy for patients (pts) with chronic Hepatitis C (HCV) who have previously failed IFN-based therapies is not fully known.

Objective:

To compare the safety and efficacy of continuous weight-based (CONT) vs. Categorical weight-based (CAT) PEG-IFN alfa-2b/RBV in patients who have failed to achieve sustained virologic response after previous IFN/RBV treatment.

Methods:

This is an open-label, multi-center, randomized clinical trial of CONT vs. CAT PEG/RBV. Patients were randomized to receive 800mg RBV QD with either Continuous weight adjusted PEG-IFN alfa-2b (1.5 mcg/kg) QW (n=259) or Categorical weight adjusted PEG-IFN alfa-2b (100 mcg if < 80kg, 150 mcg if > 80kg) for 48 weeks. HCV RNA was evaluated at baseline (BL), week 12 (EVR), and end of treatment (EOT).

Intent-to-treat response rates were compared using Fischer's Exact Test and logistic regression.

Results:

- ◆ 517 patients were enrolled and took at least one dose of drug.
- ◆ The median age was 47 years, and the patients were 64.8% male,
- ◆ 76.8% Caucasian, 13.5% Black and 8.3% Asian.
- ◆ HCV Genotype 1, 90.5% and 2 or 3, 9.5%.
- ◆ 207 pts completed 48 weeks of treatment.
- ◆ 278 pts withdrew before EOT; the primary reason for withdraw was viral non-response.
- ◆ No differences were observed in adverse events between treatment groups, including neutropenia (p=0.7).
- ◆ EVR/EOT for CONT and CAT were 40.0%/24.3% and 31.0%/25.6%, respectively (p=0.47 and 0.64).
- ◆ EVR/EOT for relapsers and non-responders were 50.6%/34.9% and 23.9%/20.3%, respectively (p < .0003).
- ◆ EOT response was 23.8% in genotype 1 and 36.7% in genotype 2/3(p=0.046).

Conclusions:

Continuous and Categorical weight-based dosing of PEG-IFN alfa-2b/RBV had similar safety and efficacy in the re-treatment of patients who failed or relapsed after original IFN-based therapy for HCV. Among non-responders to prior therapy, the end of treatment response was more than 20%; as expected the end of treatment response was higher among relapsers. These data suggest that PEG-IFN alfa-2b/RBV may be effective in persons who initially failed to respond to or relapsed after previous IFN/RBV treatment.

Abstract 1293

Pegylated Interferon Alfa 2b and Ribavirin for Hepatitis C Patients Who Were Nonresponders to Previous Therapy

Eric J. Lawitz, N. S. Bala, Scott Becker, Geri Brown, Mitchell Davis, Ravi Dhar, K. P. Ganeshappa, Stuart Gordon, Kent Holtzmuller, Mark Jeffries, Jianjun Li, Howard Monsour, Pierre Nader, Thomas Rosenfield, Keith Tolman, Shailesh Kadakia, Alamo Study Group

Background:

There are currently no accepted treatment options for standard combination therapy nonresponders. Viral kinetics studies have shown an early dose dependent phase of viral clearance. The induction strategy was introduced based on this data but trials have not shown a benefit to this strategy, however these trials have not followed induction with continuous interferon for the entire 48 weeks. Pegylated interferon (PEG-IFN) allows a convenient mechanism to deliver continuous interferon, possibly making the induction strategy more successful. Aim: To evaluate the efficacy of induction PEG-IFN and ribavirin compared to fixed dose PEG-IFN and ribavirin in previous standard combination therapy nonresponders, IFN monotherapy nonresponders, and combination therapy relapsers. Methods: Participants were randomized to receive either PEG-IFN 1.5 mcg/kg/wk + Ribavirin (Riba) 1000-1200mg daily x 12 weeks then PEG-IFN 1.0mcg/kg/wk + Riba 800mg x 36 weeks or PEG-IFN 1.0 mcg/kg/wk + Riba 800 mg for 48 weeks. HCV-RNA was measured at weeks 0, 24, 48, and 72.

Results:

Four hundred and eight six previous combination therapy nonresponders, 116 IFN monotherapy nonresponders, and 125 combination therapy relapsers with compensated liver disease were enrolled.

Baseline characteristics include: Genotype 1-85%, African Americans-17%, and advanced liver disease-42%. Three hundred and seventeen combination therapy nonresponders (Combo NR), 75 interferon monotherapy nonresponders (Mono NR) and 68 combination therapy relapsers (Combo Relapser) have reached week 72. Results are seen in the table below. Therapy was terminated early in 20% of fixed dose and 21% of induction participants.

Conclusion:

Interim results suggest the use of induction dosing does not improve the sustained response rates in the three groups evaluated. Previous combination nonresponders achieve a sustained response in 5-10% of participants. Complete sustained response data including an analysis of partial responders to previous therapy will be presented at the annual meeting.

<i>Treatment Group</i>	<i>Combo NR</i>		<i>Mono NR</i>		<i>Combo Relapser</i>	
	Induction	Fixed	Induction	Fixed	Induction	Fixed
<i>SVR</i>	10% (16/160)	5% (7/157)	14% (5/35)	13% (5/40)	20% (6/30)	26% (10/38)
<i>Genotype 1</i>	8% (11/143)	4% (6/139)	9% (2/23)	12% (4/34)	18% (4/22)	12% (3/25)
<i>Stage 3-4</i>	4% (3/76)	3% (2/70)	17% (3/18)	8% (1/13)	15% (2/13)	16% (3/19)
<i>African American</i>	0% (0/35)	3% (1/32)	25% (1/4)	0% (0/8)	0% (0/2)	0% (0/2)