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Alan Franciscus
Editor-in-Chief, HCV Advocate



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The following oral presentations followed the Plenary Session moderated by Dr. Norah Terrault and Dr. Mitchell Schiffman. These presentations were moderated by Dr. Karen Lindsay and Dr. Paul Kwo.

Pegylated Interferon Alfa-2b (PEG-IFN) Plus Ribavirin Versus PEG-IFN for Treatment of HIV/HCV Co-infected Patients (pts): An Open, Multicenter, Randomized Trial

A. Cargnel, A. Casella, E. Angeli, G. Gubertini, G. Orlando, P. Duca, and ICOS (Italian Coinfection Study) Group, Milan, Italy

Highly active antiretroviral therapy (HAART) has improved the life expectancy of pts with HIV, thus favoring the evolution of HCV infection. The author reported that in 1990 the incidence of HIV+ patients dying from liver disease was 5% and that this rate has risen to 38% in 2000. In HIV-positive pts, HCV infection is more severe, so its treatment in co-infected pts is critical. While PEG IFN + ribavirin has become the standard treatment for HCV in HIV-negative pts, little is known about its profile in co-infected pts. Objective: To evaluate the efficacy and safety of PEG-IFN + ribavirin vs PEG-IFN alone in co-infected pts receiving HAART.

Pts were randomized in an open, multicenter study. Group A received PEG-IFN 1.5 µg/kg weekly + ribavirin 800 mg daily for 48 weeks; Group B received PEG-IFN alone. Inclusion criteria included stable HIV RNA (<400 cp/mL), CD4+ cell count (300 cells/mm³ or greater), and no prior HCV therapy. Laboratory monitoring was performed monthly; quantitative/qualitative HCV RNA assessments were performed at regular intervals.

To date, 49 pts have completed at least 24 weeks of therapy, 5 of which had cirrhosis. Virologic response (negative for HCV RNA PCR) was observed in 17 pts (34.7%; 14/25 pts in Group A, 3/24 in Group B). 56% (14/25) of patients were HCV RNA negative at 24 weeks in an on-treatment analysis (did not take into consideration the patients that had to drop out of the study due to side effects). Pts infected with non-1 HCV genotype in both groups showed significantly better responses than those with genotype 1. CD4+ cell counts were slightly decreased at Week 24 (581 at week 0 and 452 at week 24), but there was no increase in HIV RNA except for in one patient who underwent a change of HAART. Therapy was discontinued in 28% of the patients due to intolerance or flu-like symptoms (13.2%), compliance (6.9%), hematologic toxicity (5.7%), or rash (1.6%). The discontinuations all occurred in the first 4-6 weeks of therapy. If the author of this study had included these discontinuations in the failure rate as is done in a true intent-to-treat analysis the 56% response rate at week 24 would be significantly reduced. PEG-IFN dose was reduced to 0.5 µg/kg in 12 pts;

ribavirin to 600 mg/day in 2 pts. Only 1 pt had an increase in ALT levels at 6 mos, when nevirapine was introduced. Consistent in what has been demonstrated in other studies, patients who experienced a steep slope decline of HCV viral load in the first month were much more likely to be responders by 24 weeks. Neither life-threatening adverse events nor lactic acidosis occurred independent of HAART.

In summary, PEG-IFN + ribavirin seems to be effective and well tolerated in the treatment of HIV/HCV pts. Considering these preliminary results and the effect of HCV in HIV-positive pts, this therapy should be recommended in those pts with a conserved immune status.

Pegylated Interferon alfa-2b and Ribavirin for the Treatment of Chronic Hepatitis C Infection in African Americans and Non-Hispanic Whites. A Preliminary Report.

Andrew J. Muir, Jeffrey D. Bornstein, Paul G. Killenberg, Southeastern Hepatitis Treatment Group, Durham, NC

Previous studies have suggested lower response rates for African American patients treated for chronic hepatitis C infection with interferon alpha-based regimens. In a study by Reddy et al published in Hepatology 1999 there was a 2% SVR seen in a study of 40 African American patients. Higher prevalence of genotype 1 infection among African Americans has been suggested as a potential explanation for the lower response rates. All of these studies, however, included few African American patients. Thus, no study to date has definitively determined if response rates diverge between African American and non-Hispanic white patients. Objective: To compare the sustained virologic response rates of African American and non-Hispanic white patients with chronic hepatitis C infection treated with pegylated interferon alfa-2b and ribavirin.

Patients were enrolled into dual cohorts of African American and non-Hispanic white patients with chronic hepatitis C infection. Exclusion criteria included decompensated liver disease and any previous therapy with interferon alpha. All patients received pegylated interferon alfa-2b 1.5 mcg/kg per week for 48 weeks plus ribavirin 1000 mg/day x 12 weeks followed by 800 mg/day for 36 weeks. Results: One hundred patients were enrolled into each cohort. The baseline characteristics of the African American group were: 67% male, mean age 47.5 years, and mean duration of infection 19.3 years. The baseline characteristics of the non-Hispanic white group were: 53% male, mean age 44.2 years, and mean duration of infection 18.8 years. In both groups, 98% of the patients had genotype 1 infection. The African American patients had a greater mean weight (89.0 vs. 81.6 kg, $p = 0.01$) and a greater prevalence of diabetes mellitus (23% vs. 6%, $p < 0.001$). Abnormal ALT's were not part of the inclusion criteria however no patients enrolled had normal ALT's. This is interesting as in previous studies there have been suggestions that African American patients have disproportionately been represented due to a higher incidence of normal ALT's among African Americans. The main reason for being excluded in the non-African American group was not having genotype 1 hepatitis C.

To date, 168 have completed at least 12 weeks of therapy, and 139 patients have completed at least 24 weeks. The results are summarized in the table. The complete 24-week results will be presented at the meeting. Conclusions: These preliminary results suggest a lower response rate among African American patients when compared to non-Hispanic white patients. These findings do not suggest that the lower response rate is related to the genotype. The findings support the need for continued investigation examining the explanation for the lower response rate among African American patients with chronic hepatitis C infection. A couple of postulations could be that the African American patients were considerably heavier and steatosis of the liver was not ruled out.

	African Americans	Non-Hispanic Whites	
HCV RNA negative 12 weeks	20/77 (26.0%)	52/91 (57.1%)	p < 0.001
HCV RNA negative 24 weeks	12/55 (21.8%)	52/84 (61.9%)	p < 0.001

Sampling Variability on Percutaneous Liver Biopsy in Patients with Chronic Hepatitis C Virus Infection.

Iqbal Siddique, Hisham El-Naga, John P. Madda, Fuad Hasan, Safat, Kuwait

Sampling variability on liver biopsy has been demonstrated in a variety of liver diseases. The aim of this study is to determine if sampling variability exists in patients with chronic HCV infection.

Twenty patients with chronic HCV infection, elevated liver enzymes and HCV-RNA in blood were selected for the study. There were no other concurrent liver diseases in any of the patients. Percutaneous liver biopsies were performed and two separate tissue samples were obtained from the right lobe of the liver, through the same skin puncture site. However, the orientation of the biopsy instrument was changed by 30° to 45° between the two biopsies to ensure that the samples were taken from different parts of the right lobe. The biopsies were reviewed by a single pathologist and scored using the Knodell's Histological Activity Index (HAI, range 0-22), which assesses the degree of necroinflammatory activity (grade, range 0-18) as well as fibrosis (stage, range 0-4). The two sets of biopsies were compared for differences in the total HAI score as well as the scores for necroinflammatory activity and fibrosis.

Two adequate biopsy samples were obtained in 19 patients (17 males; mean age 44.7 ± 9.0 yrs). There were no biopsy related complications in any patient. The mean serum alanine aminotransferase (ALT) was 117.3 ± 60.6 IU/L (normal 10 – 60 IU/L). The mean difference between the two sets of biopsies was 3.0 ± 2.6 (range 0 – 9) for the HAI, 2.4 ± 2.2 (range 0 – 7) for necroinflammatory activity (grade), and 0.5 ± 0.9 (range 0 – 3) for fibrosis (stage). Thirteen (68.4%) patients had a difference of ≥ 2 both in the total HAI and the necroinflammatory activity score, while 9 (47.3%) of these patients had a difference of ≥ 3. Six (31.5%) patients had a difference of ≥ 1 in the fibrosis score, while 3 (15.7%) of these patients had a difference of ≥ 2. These same 3 patients also had the highest degree of difference in the HAI (mean difference 7.6).

Sampling variability exists on percutaneous liver biopsy in patients with chronic HCV infection, both for the degree of necroinflammatory activity as well as fibrosis.

The Impact of Intervening Substance Abuse on Hepatitis C Treatment Outcomes in Recovering Injection Drug Users: An Interim Analysis

Diana L. Sylvestre, Barry J. Clements, Oakland, CA

There are 1,000,000 heroin users in the United States mostly who use needles. Among IDU's there is a 65-95% seroprevalence rate for hepatitis C. 60% of all the new cases of hepatitis C are among IDU's. To date IDU's have been excluded from the majority of trials for hepatitis C. In addition it has been reported that the recidivism rate among IDU's that are not maintained on agonist methadone maintenance therapy is 80% in the first year and 90% by the end of the second year. Treating hepatitis C in active injection drug users (IDUs) is a controversial topic. Despite their high prevalence of HCV, there are little data on the impact of alcohol ingestion, length of sobriety, and intervening drug use on treatment outcomes with interferon/ribavirin combination therapy in this population.

To date over 1000 patients have been screened and 120 have initiated therapy. The results are available for

fifty-seven recovering injection drug users enrolled in a methadone maintenance program treated with interferon/ribavirin combination therapy at standard dosing regimens. African Americans account for 27%, Latino 15% and Caucasians 57% of the total patients. The average age is 47 years and the patient population is comprised of 51% male who have been infected with HCV for approximately 29 years as determined by when injecting was initiated. Substance abuse behaviors were assessed by patient self-report as well as urine toxicology testing.

The overall end-of-treatment response rate (ETR) in this population was 54%, with a treatment discontinuation rate of 22%. Those who drank alcohol during treatment (n=12) exhibited a trend toward reduced treatment efficacy when compared with those who didn't (n=45), with ETRs of 67% and 42%, respectively (p=0.13). Although those with brief drug sobriety (<6 mo., n=9) appeared to have similar ETRs to those with more extended sobriety (n=37), 56% vs 62%, respectively, subjects without pretreatment drug sobriety (n=11) showed a trend toward a reduced ETR of 36% (p=0.15). Subjects who used injection drugs during treatment (n=17) showed a trend toward reduced ETRs when compared to nonusers (n=40), 62% vs 45% (p=0.11). However, when drug use was quantified, regular injection drug use (n=7) impacted dramatically upon treatment outcomes, with none of the daily injection drug users exhibiting a positive ETR (p=0.02). The impact of marijuana use was not associated with other drug use and did not impact adherence significantly. If during treatment patients felt like they were in withdrawal it was recommended that their methadone dose be increased. In fact, 42% of the patients had an increase of 10mg in their methadone therapy during treatment for hepatitis C. Of the patients that have completed 72 weeks of evaluation the overall SVR in this difficult to treat population is 28% compared to 41% as seen in the general HCV population. Keep in mind though that these results include all patients even those that were using drugs on a daily basis, none of which achieved an SVR so if patients are selected appropriately, better results can be anticipated.

Intervening alcohol use and lack of pretreatment drug sobriety appear to lead to modest reductions in hepatitis C treatment efficacy. However, regular injection drug use during treatment has a substantial negative impact upon HCV treatment outcomes. Further study is needed to more fully understand the impact of these behaviors on HCV treatment.

Alpha Feto-Protein Levels in Hepatitis C Subjects Treated with Combination Therapy: Abnormal Levels Decline with Therapy

Matthew J. Hepburn, Eric J. Lawitz, Alamo Study Group, San Antonio, TX

Patients with hepatitis C infection and advanced liver disease are routinely screened for hepatocellular carcinoma (HCC) with alpha fetoprotein (AFP) levels. AFP can be abnormally elevated in patients with hepatic injury but no evidence of HCC. Prior studies have correlated higher AFP levels with fibrosis in patients with hepatitis C, but no prior study has examined the effect of combination interferon and ribavirin therapy on AFP levels.

Data were retrospectively analyzed from 3 interferon/ribavirin therapy trials. The following baseline characteristics were recorded: gender, ethnicity, age, histologic stage, genotype, body mass index, HCV RNA viral load, and ALT. Viral clearance at 12 or 24 weeks of therapy was also noted. AFP was drawn at baseline and every 3 months while on therapy at our institution. Data were analyzed with multiple measures ANOVA, and paired t-tests as appropriate. A multiple linear regression model was utilized to assess baseline characteristics independently associated with AFP levels.

An initial AFP was available on 195 subjects. The overall mean AFP was 8.8 ng/ml (range 1.1 to 156 ng/ml). Thirty (15%) subjects had AFP >10 ng/ml, which is elevated at our laboratory. Among subjects with a normal baseline AFP, the level declines from 3.6ng/ml initially to 3.2 ng/ml at 3 months and 3.2 ng/ml at 6 months. For subjects with abnormal baseline AFP values, these mean levels declined from 24.1 ng/ml to 9.4ng/ml at 3 months to 8.0 ng/ml at 6 months (p<0.05). During therapy, 21/27 (78%) subjects with an elevated baseline AFP normalized to a level below 10ng/ml. Subjects with viral clearance had a lower baseline mean value (4.5

ng/ml) compared to the baseline value of subjects who were unable to achieve viral clearance (12.2 ng/ml). In subjects that did not achieve viral clearance, the mean AFP declines significantly, from 12.2 ng/ml to 5.5 ng/ml ($p < 0.05$). On multivariate analysis, histologic stage was independently associated with AFP ($p = 0.03$).

In summary, in subjects with hepatitis C treated with combination therapy, abnormal baseline AFP levels substantially decline, usually to below 10ng/ml. Subjects unable to achieve viral clearance on therapy also have a significant decline in AFP.

Does Normal ALT Exclude Severe Hepatic Fibrosis in Patients with Chronic Hepatitis C?

Mohamed A. Metwally, Claudia O. Zein, Nizar N. Zein, Rochester, MN

It has been suggested that chronic HCV patients with persistently normal ALT values tend to have minimal histologic activity or fibrosis. Treatment of these patients is therefore still controversial.

The aims of this study were to:

1. Study the prevalence of normal ALT at the time of first evaluation in patients with chronic HCV.
2. Assess the relationship between hepatic fibrosis, inflammatory activity, and normal ALT in HCV patients.

198 previously untreated consecutive patients with chronic HCV were included. All patients had serological, virological, and histological evidence of chronic HCV. Patients with any other confounding chronic liver disease were excluded. Demographic and laboratory data were collected for each patient at the time of liver biopsy. Data of liver biopsy including degree of activity, stage of fibrosis and degree of steatosis were also collected. Patients with normal ALT were identified and follow up data for ALT were collected to identify those with persistently normal values.

Normal ALT at the time of first evaluation was found in 25 out of 198 patients (12.7%). There was no significant difference between patients with normal ALT and patients with high ALT regarding gender, age at infection time, duration of infection and route of acquisition. Patients with normal ALT had lower AST level ($P = 0.0005$), lower serum bilirubin ($P = 0.01$), lower serum iron ($P = 0.003$) and lower body mass index ($P = 0.03$). Severe hepatic fibrosis (stage III, and IV) was found in 52/173 (30%) patients with high ALT compared to 6/25 (24%) patients with normal ALT ($P = 0.5$). Hepatic inflammatory activity was substantially less in patients with normal ALT compared to those with high ALT ($P = 0.03$). Follow up data for 18 normal ALT patients showed that only 7 (39%) had persistently normal ALT values. Results did not change when comparing those with persistently normal ALT to patients with high ALT.

In summary:

- ◆ A single normal ALT value at the time of first evaluation is relatively common in chronic HCV patients.
- ◆ Most patients with a normal ALT value at the time of first evaluation did not have a persistently normal ALT.
- ◆ Patients with normal ALT (single time or persistently) tended to have lower body mass index and hepatic inflammatory activity but were not less likely to have severe hepatic fibrosis.
- ◆ A normal ALT in chronic HCV patients should not preclude liver biopsy examination or therapy.