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The Digestive Disease Weekly Conference is being held in San Francisco from May 19 – 22, 2002. This report begins the HCV Advocate's daily coverage of clinical data related to hepatitis C. These reports will focus on live plenary presentations with a summary of posters and abstracts to follow upon completion of this daily conference coverage.



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African-Americans with Chronic Hepatitis C Respond Poorly to Interferon/Ribavirin Combination Treatment Even When Induction Regimens are Used.

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Response to treatment in patients with chronic hepatitis C (CHC) is influenced by many factors. Genotype, level of viremia, degree of inflammation and fibrosis are some of the known factors. It has recently been described that African-Americans (AA) respond poorly to treatment of CHC infection as compared to Caucasians.

The aim of this study is to compare the treatment response in AA and Caucasian patients with CHC and to determine if giving induction doses (5 million units daily) of Interferon (IFN) during the initial 4 weeks of treatment improved response to treatment.

A total of 93 (AA=62, Caucasians = 31) patients were randomized to three study arms according to race. In the first arm, patients received 3 MU of INF tiw along with ribavirin. In the second arm, patients were given 5 MU tiw and ribavirin every day for 4 weeks followed by IFN at 3 MU tiw and ribavirin. In the third arm, 5 MU of INF was given everyday along with ribavirin for 4 weeks followed by IFN at 3 MU tiw of INF and ribavirin. The dose of ribavirin was either 1000 mg or 1200 mg based on patient's weight below or above 75 kg, respectively. Patients who tested positive for HCV RNA by PCR at week 24 of treatment were considered non-responders and treatment was discontinued. Those negative for HCV RNA were continued on treatment for another 24 weeks if genotype 1, while those with genotype 2 and 3 had their treatment discontinued.

This was an intent to treat analysis. Of the 93 patients enrolled, 25 had treatment discontinued either due to non-compliance (n=16, A.A=9, Cauc.=7), side effects (n=7) or health insurance problems (n=2). There was no statistically significant difference in end of treatment response (ETR) in the three treatment arms (20%, 24% and 24% respectively). While the overall ETR was 22.5% (n=21), ETR for Caucasians was significantly

higher ($p < 0.0001$) at 51.6% ($n=15$) compared to 9.6% ($n=6$) in AA. Genotype distribution and randomization to the 3 treatment arms was similar in both groups.

In summary, African-Americans with CHC respond poorly to combination IFN and ribavirin treatment as compared to Caucasians. Induction with high dose IFN does not improve response to therapy in either A.A's or Caucasians.

Long-Term Efficacy of Dose Intensified Interferon alpha 2b and Ribavirin Therapy for Hepatitis C in HIV-Coinfected Patients

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The natural course of hepatitis C is accelerated in patients with concomitant HIV infection. Therefore treatment strategies are urgently needed for this patient group. With availability of data showing superior treatment responses for patients with hepatitis C with IFN and RBV combination therapy, the question arose whether this therapy would also be effective in HIV/HCV coinfecting patients. Therefore we evaluated the long term efficacy, tolerance and safety of dose intensified IFN alpha 2b + RBV for the treatment of chronic hepatitis C in HIV -coinfecting patients in an open prospective study. The inclusion criteria were as follows:-

- ◆ Elevated liver transaminases $> 1.5X$ UNL (GPT $> 40U/l$)
- ◆ Naïve for anti-HCV therapy
- ◆ Positive HCV antibodies and HCV-RNA
- ◆ Stable HIV infection with $CD4 > 200/\mu l$
- ◆ Age > 18 years and written consent

Methods: 23 HIV/HCV-coinfecting patients (median age: 41,5 [range 20; 57]); 18 male and 5 female were treated for 2 weeks with RBV (600 mg/bid) alone to assess changes in endogenous IFN levels. All patients were naïve for anti-HCV therapy. Subsequently, patients received IFN (5 million units qd) plus RBV (600 mg/bid) for the next 10 weeks. Thereafter patients received standard IFN (3x5 MIU/tiw) in combination with RBV (600 mg/bid) up to week 48. 14 of the patients (61%) received concomitant highly active antiretroviral therapy.

The following measurements were performed at baseline and week 12, 24, 36 and 48 weeks:-

- ◆ Quantitative HCV-RNA
- ◆ Liver transaminases
- ◆ Absolute and relative CD4 count
- ◆ HIV-RNA

The results were as follows:-

Patient Characteristics

- ◆ 23 HIV/HCV coinfecting patients
- ◆ median age = 41.5 (range 20;57)
- ◆ female = 5, male = 18
- ◆ 14 patients received HAART regimens
- ◆ 1 NRTI = 4 (21%)
- ◆ 1 NRTI + 1PI = 1 (7%)
- ◆ 2 NRTI + 1PI = 2 (14%)

- ◆ 2 NRTI + 2PI = 1 (7%)
- ◆ 2 NRTI + 1NNRTI = 6 (42%)
- ◆ Risk Factors
- ◆ IVDU (n=15)
- ◆ Hemophiliac (n=3)
- ◆ Homosexual (n=2)
- ◆ Heterosexual (n=1)
- ◆ Work-related (n=1)
- ◆ Unknown (n=1)
- ◆ HCV genotype
- ◆ 1a = 10
- ◆ 1b = 2
- ◆ 1a/1b n = 1
- ◆ 3 n = 9
- ◆ 4 n = 1

48% of the patients had a HCV genotype 1 infection.

Within the first two weeks of therapy no significant change in endogenous IFN levels were observed ($p = 0.3506$). After 3 months of IFN/RBV combination therapy early biochemical and virological response (defined as HCV RNA < 600 copies/ml = limit of detection) was observed in 10/23 (43%) of the patients. 8 of 23 (35%) patients had non detectable HCV viremia after 6 months of treatment. 6 (26%) of the primary responders did not complete 48 weeks of therapy and 3 (13%) of patients showed a renewed increase of HCV-RNA.

7 (7%) patients did not show virological response and were discontinued from treatment after 12, 24 and 36 weeks. 20/23 (87%) patients discontinued treatment before week 48. Reasons for treatment discontinuation were: virological non-response (n=10), severe IFN-related side effects (n=2), anemia (n=2), pancreatitis (n=1), depression/aggression (n=3), severe CD4 count decrease (n=1) and active substance abuse (n=1).

3 individuals were PCR-negative at the end of therapy (week 48) leading to an EOT response of 13%. Six months later the 3 patients remained HCV PCR negative resulting in an SVR of 13%. Table 1 summarizes the patient disposition at week 12, 24, 36 and 48.

Table 1

	<i>Week 12</i>	<i>Week 24</i>	<i>Week 36</i>	<i>Week 48</i>	<i>SR</i>
On study	18	15	10	3	3
VR	10	8	5	3	3
Virological failure	2	4	4	-	-
Adverse events	1	1	3	-	-

A dose reduction for RBV from 1200mg/day to 600mg/day was necessary in 12/23 (52%) due to adverse events (hemolysis n=6)

A significant change ($p > 0.01$) in HCV RNA could be observed and also a significant decline in ALT/AST. Absolute CD4 count fell from median baseline 537 (range 316;1225) cells/ μ l to 370 (167;659) cells/ μ l at week 24 ($p < 0.03$). In parallel HIV RNA changed from baseline 995 (50;152,900) copies/ml to 1,990 (50;210,000) copies/ml at week 24. However this change was not statistically significant.

No virological failure was observed for HIV antiretroviral therapy, no switch of HAART was necessary, during the study period.

In summary, sustained response following 48 weeks of dose intensified interferon/ribavirin combination treatment is low in HIV/HCV-coinfected patients due to a high discontinuation rate from adverse events and virological failure/non-response.

- ◆ After 24 weeks of IFN/RBV treatment 35% of the patients showed a virological response
- ◆ No significant change of HIV RNA were observed during treatment of IFN +RBV
- ◆ SR following dose intensified IFN/RBV combination treatment is low in HIV/HCV coinfectd patients due to a high drop out rate. (87%) up to 48 weeks
- ◆ The results suggest that the dose intensification of IFN is associated with significant toxicity in HIV/HCV coinfectd patients and thereby limits positive treatment success.

Higher Dosing of Ribavirin (>14MC/KG) Increases Risk of Anemia without Improving Viral Response

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Background:

High dose of ribavirin may improve viral response but also may increase the risk of anemia and withdrawal from therapy.

The optimal dose for Ribavirin for maximal effect and minimal anemia has not been well described.

It is also unknown if PEG-IFN, compared to standard IFN, will result in more anemia due to its more potent impaired compensatory reticulocytosis (an increased number of immature red blood cells in circulating blood).

A total of 124 patients with chronic hepatitis C were evaluated. Hemoglobin levels in patients treated with PEG-IFN alpha 2b combined with ribavirin (800-1400mg per day) vs. standard INF alpha 2b + ribavirin (800-1400mg per day) were analyzed. Per standard criteria for combination therapy, all patients had Hb level >12g/dl for female or 13g/dl male patients at the time of enrollment. Anemia was defined as Hb<10.6g/dl. Pretreatment liver histology and serum hepatitis C virus RNA were examined. HCV viral sustained response was assessed.

Table 1. Patient Characteristics

	<i>INF+ Ribavirin</i>	<i>PEG-IFN alpha 2b + Ribavirin</i>
Patient No.	54	70
Age	45	46
Male	48%	51%
Genotype 1	72%	69%
AST	77 +/- 14	70 +/- 6
ALT	61 +/- 18	58 +/- 9
Fibrosis stage	3.87 +/- 0.24	3.93 +/- 0.18

Table 2. Patient characteristics between anemia and non-anemia groups

	<i>Anemia</i>	<i>Non-Anemia</i>
Patient No.	14	110
Age	51	46
Male	28%	48% (P<0.05)
Genotype 1	64%	71%
AST	75 +/- 14	72 +/- 6
ALT	64 +/- .18	55 +/- 9
Fibrosis stage	4.9 +/- 0.48	3.8 +/- 0.15 (P<0.05)

Table 3. Rate of HCV Viral Response to Therapy (HCV <600 at 12 wks)

<i>Anemia</i>	<i>Non-Anemia</i>
50%	44%
INF + Ribavirin	PEG-INF alpha 2b
29%	50% (p<0.05)

The Incidence of Anemia in Men and Woman at 12 Week Treatment

<i>Men</i>	<i>Woman</i>
6%	18%

The incidence of anemia was significantly higher in women than men at 12 weeks of combination therapy of IFN and Ribavirin (p<0.05)

Comparison of the incidence of Anemia at 12 Week between Treatment Groups

<i>INF + Ribavirin</i>	<i>PEG-INF + Ribavirin</i>
8%	16%

Comments: There was a significantly increased incidence of anemia in patients treated with PEG-INF alpha 2b + ribavirin compared to standard INF alpha 2b + ribavirin at 12 week treatment (p<0.05)

A Drop of Mean Hb (gm/dl) in Treatment Groups

<i>INF + Ribavirin</i>	<i>PEG-INF + Ribavirin</i>
Approximately 1.75	Approximately 2.5

Comments: There was a significant drop of mean Hb in HCV patients treated with PEG-INF alpha 2b + ribavirin compared to standard INF alpha 2b + ribavirin at 12 week treatment (p>0.05)

Comparison of Ribavirin Dosage per kg by Body Weight between Anemic and Non-anemic groups

<i>Anemia</i>	<i>Non-Anemia</i>
14	12

Comments: The Ribavirin dosage per kg by body weight in anemic patients was significantly higher than that in non-anemia patients at 12 weeks treatment (p<0.05)

In summary:

- ◆ Female gender and increase in fibrosis stage were associated with increased incidence of treatment induced anemia.
- ◆ Combination of PEG-INF + Ribavirin increased the incidence of anemia compared to standard IFN + Ribavirin.
- ◆ Higher Dosing of Ribavirin (>14mg/kg) does significantly increase risk of anemia without significantly improving viral response.
- ◆ Further research is needed to evaluate strategies to minimize treatment-associated anemia and

maximize therapeutic efficacy.