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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.

May 19, 2002

The following oral presentations were given on the afternoon of the first day of DDW. The first six presentations were moderated by Dr. Norah Terrault and Dr. Mitchell Schiffman.

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

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Pegylated interferons have proven superior to standard interferons as monotherapy for chronic hepatitis C and, more recently, in combination with ribavirin (RBV) in treatment-naive patients. Currently 60% of the patients that were treated with standard interferon and ribavirin (Rebetron) are either non-responder or relapsers looking for additional options for treatment.

The aim of this study is to compare the efficacy of two dose regimens of pegylated interferon alfa-2b plus ribavirin in patients with prior non response to interferon (IFN) monotherapy or combination therapy, or with relapse after combination therapy.

Patients in the three categories are randomized in this ongoing trial to receive pegylated interferon alfa-2b 1.0 ug/kg plus RBV 1000-1200 mg/d with patients >75kg receiving 1200mg/day of ribavirin and patients <75kg receiving 1000mg/day of ribavirin (Group 1), or pegylated interferon alfa-2b 1.5 ug/kg plus ribavirin 800 mg/d (Group 2) which is the currently approved dosing regimen by the FDA.

Prior therapy must have been stopped at least three months prior to entry. Treatment is planned for 48 weeks, with cessation of therapy if PCR for HCV RNA (Roche Amplicor) remains positive at 24 weeks. The inclusion criteria had no ALT restriction. The average age of the patients was 49 with an average fibrosis score by Metavir of 2.2. 87% of the patients were genotype 1 in both groups compared to 7-9% genotype 2. Approximately 75% of the patients were male and generally both groups well represented the general population with hepatitis C. Approximately 70% in each group had a viral load > 1 million copies/ml and approximately 40% of patients had stage 3 or 4 fibrosis.

In the genotype 1 non-responders to previous combination therapy there was an SVR of only 10% in Group 1 and 11% in Group 2. The preliminary results of this study are based on only 49/160 in Group 1 being available for evaluation at week 72 and only 35/160 in Group 2. The EOT response at 48 weeks for genotype 1 was 10% in Group 1 and 20% in group 2. This was consistent with the 24 week data which showed 16% HCV RNA negative in Group 1 versus 29% in Group 2. Despite this early separation in the groups there was considerably greater relapse in Group 2 since the SVR results were very similar that the author thought could be attributable to needing greater than 800mg of ribavirin. The overall SVR in patients that had been relapsers (instead of non-responders) to previous therapy was 43% in group 1 and 60% in group 2 even though the numbers of patients being evaluated were too small to draw conclusions. The overall SVR for patients that were non-responders to interferon monotherapy was 40% in group 1 and 25% in group 2.

In summary this study demonstrates a high percentage of breakthrough and relapsers as witnessed by the SVR's being so much lower than the early 24 week PCR negative results. The author said that about 35% of patients need a dose reduction and that a factor that increased likelihood of response was a low viral load at the end of a patient's prior treatment. Other factors that the author pointed out was that normal ALT's did not impact response, higher doses of pegylated interferon alpha 2b were needed in patients with more advanced disease. *Additionally the author commented that greater than 12 months of therapy might be needed in these types of patients that are intrinsically resistant to therapy.* When asked how African Americans responded in the trial, the presenter stated that in genotype 1 African Americans the SVR was 1/12 (8%) versus 17/87 (20%) in Caucasians.

Pegylated Interferon Alfa 2b (PEG-IFN) and Ribavirin for Hepatitis C Patients who Were Nonresponders to Previous Therapy

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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. PEG-IFN allows a convenient mechanism to deliver continuous interferon, possibly making the induction strategy more successful.

The aim of this study is 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 1000-1200mg daily x 12 weeks then PEG-IFN 1.0mcg/kg/wk + Ribavirin 800mg x 36 weeks or PEG-IFN 1.0 mcg/kg/wk + Ribavirin 800 mg for 48 weeks. HCV-RNA was measured at week 0, 24, & 48 of treatment and 24 weeks post treatment. Results: Five hundred and one previous combination therapy nonresponders, 122 IFN monotherapy nonresponders, and 130 combination therapy relapsers with compensated liver disease were enrolled. Baseline characteristics include: Genotype 1-84%, African Americans-17%, and advanced liver disease-43%. Two-hundred and sixty five combination therapy nonresponders (Combo NR), 64 interferon monotherapy nonresponders (Mono NR) and 56 combination therapy relapsers (Combo Relapser) have completed 24 weeks of therapy. Results for 24 week and partial 48 weeks are seen in the table below. The authors additionally looked at a subset of patients defined as partial responders. Partial responders were patients that during previous therapy had = or > that a 1 log drop in HCV RNA during previous therapy. These patients had an EOT response of 46% compared to 20% in patients that had not achieved that defined previous partial response. Discontinuations in this study were approximately 22-23%. PEG-IFN was reduced in 7% while ribavirin was reduced 5-6%.

In summary, even though SVR's are not yet available interim results suggest the use of induction dosing does not significantly improve the twenty-four week or EOT viral clearance rates in the three groups evaluated, with the presenter stating no statistical significance in the EOT result between induction and fixed dosing in the combination relapser.

24 week results

	Combo NR (Induction/Fixed)		Mono NR (Induction/Fixed)	
Overall	32%	25%	45%	43%
Genotype 1	29%	21%	37%	35%
Stage 3-4	24%	22%	45%	33%
Combo Relapser				
Treatment Group	Induction		Fixed	
Overall	69%		71%	
Genotype 1	63%		67%	
Stage 3-4	66%		67%	

48 week results

	Combo NR (Induction/Fixed)		Mono NR (Induction/Fixed)	
Overall EOT	25%	15%	34%	30%
Combo Relapser				
Treatment Group	Induction		Fixed	
Overall EOT	58%		55%	

Prediction of Early Virologic Response to Treatment with 40KD Pegylated (PEG)-Interferon (IFN) Alfa2a/Ribavirin in Patients with Chronic Hepatitis C (Genotype 1)

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Response to antiviral therapy in chronic hepatitis C can be measured at various time points. The 24-hour response to a single IFN dose (24hVR) identifies IFN resistance to standard IFN/ribavirin therapy (a decrease in viral load of <0.8 log predicted non-response with 100 percent specificity; Jessner et al, Lancet 2001). Early virologic response (EVR) after 12 weeks has a high predictive value to achieve a sustained response to 48 weeks of 40kD-PEG-IFN α 2a/ribavirin therapy (Ferenci et al, AASLD 2001).

In an ongoing prospective trial which compares amantadine and placebo in addition to treatment with 180 μ g 40KDPEG-IFN α 2a (Roche, Basel, CH)/week + 1-1.2g ribavirin/d in chronic hepatitis C (genotype 1) patients are stratified according to the 24hVR (viral response) at randomization. All patients had a liver biopsy and none had received an antiviral therapy before signing an informed consent. Currently 77 of the planned 220 patients were recruited, and 33 completed 12 weeks of treatment. In these patients the 24hVR was compared with the 12 week EVR (defined as HCV-RNA neg). Analysis was done without knowing to which treatment group a patient was assigned. The 24hVR was performed 2 weeks prior randomization and was calculated from the decrease in viral load 24 hours following a single dose of 9 MU IFN α 2a (Roferon $\text{\textcircled{R}}$, Roche, Basel, CH). Viral load was determined by the Cobas Amplicor Monitor HCV Test $\text{\textcircled{R}}$, v2.0 (Roche Diagnostic Systems, USA).

Of the 33 patients 21 (63.4%) became HCV-RNA negative by week 12. The 24hVR in EVR was 1.19 (log decline) \pm 0.43 (SD) and 0.55 \pm 0.36 in non-responders ($p=0.00014$). The magnitude of the 24hVR correlated with the 12 week EVR: 7/7 (100%), 10/13 (77%), and 4/13 (30.7%) pts. with an 24hVR of >1.5 , 0.8-1.49, or <0.8 log decline, respectively, were responders ($p=0.004$).

In summary, the 24hVR is a good predictor of the 12 week EVR in patients on 40KDPEG-IFN α 2a/ribavirin therapy. A 24 hour change in viral titer >1.4 log drop has a 100% predictive factor according to the presenter. Patients with predicted poor response to standard-IFN/ribavirin therapy may still achieve a virologic response on PEG-IFN α 2a/ribavirin therapy. The presenter stated that 40% of predicted non-responder to standard interferon/ribavirin may respond to Pegasys. Thus, PEG-IFN α 2a may overcome IFN-resistance in HCV-genotype 1 patients. Prediction of response to antiviral therapy may help to optimize treatment.

Interferon Alfa-2b and Ribavirin for Patients with Chronic Hepatitis C and Normal ALT: Final Results

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Most studies establishing the role of antiviral therapy in patients with chronic hepatitis C (CHC) have excluded patients with normal ALT levels. It is estimated that anywhere from $<5\%$ to 20% of hepatitis C patients with normal ALT's have significant hepatic fibrosis. Small trials with interferon monotherapy suggested limited efficacy and/or de novo ALT elevations (treatment induced rising of ALTS) in response to treatment. There is little published data on combination therapy in these patients.

The aim of this study was to evaluate the efficacy of two doses of interferon alfa-2b (IFN) combined with ribavirin (RBV) in patients with CHC and normal ALT levels. Patients with biopsy-proven CHC who were PCR-positive for HCV RNA and at least 2 normal ALT levels 3 or more months apart were randomized to: Group 1: IFN 3 MU tiw plus RBV 1000-1200 mg depending on weight $<$ or $>$ 75 kg, or Group 2: IFN 5 MU tiw plus RBV 1000-1200 mg. Patients were treated for 24 weeks and a PCR obtained. Therapy was stopped if the PCR was positive and continued for an additional 24 weeks if the PCR was negative. A final PCR (NGI) was obtained 24 weeks after cessation of therapy.

56 patients were randomized and received at least one dose of medications; 43 (77%) received at least 24 weeks of treatment. The majority of the patients were female (60%). 15% of patients were F3/F4. The rates of sustained response (SR) in the overall study population, by treatment group, and by genotype are shown in the Table. Of 10 African-American patients, 1/10 (10%) had SR. In the overall study group, 3 patients had end of treatment response, followed by relapse, and another 3 had breakthrough relapse. There were 3 serious adverse events (MI, confusion, suicidal ideation). 4 patients developed thyroid dysfunction. 5 patients had mild, transient ALT elevations. No sustained ALT elevations were noted.

In summary:

1. Patients with normal ALT had a rate of SR only slightly lower than SR rates in patients with elevated ALT.
2. The SR rate in patients with genotype 1 approached that seen in patients with genotype 1 and elevated ALT.
3. The higher dose of interferon appeared to be more effective in patients with genotype 1 infection so this leaves open the question, what is the optimum dose?
4. Side effects were similar to those seen in other populations, and de novo ALT elevations were transient and not clinically significant.
5. *Patients with CHC should not be excluded from treatment on the basis of ALT alone.*
6. Combination therapy with peginterferon and ribavirin should be evaluated in this group of patients.

	SR	Group 1	Group 2
Overall	17/56 (30%)	7/29 (24%)	10/27 (37%), p=0.39
Genotype 1	10/42 (24%)	2/20 (10%)	8/22 (37%), p=0.07
Genotype 2	5/7 (71%)	4/5 (80%)	1/2 (50%)
Genotype 3	2/3 (66%)	1/2 (50%)	1/1 (100%)
Genotype 4	0/4 (0%)	0/2 (0%)	0/2 (0%)

Amantadine Therapy for Chronic Hepatitis C: A Randomized Double-Blind Placebo Controlled Trial

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Treatment of hepatitis C has been disappointing with less than half responding to therapy with interferon and/or interferon and ribavirin and most experiencing untoward side effects. The purpose of the present study was to evaluate the safety and effectiveness of oral amantadine for the treatment of chronic hepatitis C.

The study was designed as a prospective double-blind randomized placebo-controlled trial where patients were randomized according to age, gender, HCV RNA level, severity of liver histology, and whether they had received prior interferon therapy. Subjects received either amantadine 100 mg twice daily by mouth or placebo for 6 months. After 6 months, all patients were treated with amantadine for an additional 6 months such that half of the patients received 6 and half received 12 months of amantadine. Patients were followed for 6 months after termination of drug to evaluate the rate of sustained response.

152 patients were treated including 7 children. The patients were made up of 144 Caucasians, 2 Hispanic and 6 African Americans. Of the 152 patients treated, 117 were males. Compared to placebo, 27% of subjects responded to amantadine with loss of HCV RNA and normalization of ALT (p=0.03). 64% of patients experienced a decrease in ALT. Response rates were 27% and 22% for 12 versus 6 months of therapy, respectively. The overall sustained response rate 6 months after cessation of amantadine and confirmed by qualitative PCR was 15.6% (19.4% at 12 months and 12% at 6 months). The following pretreatment characteristics favored a response: female gender, low HCV RNA level, age greater than 50

years, severe liver histology (F3/4), and genotype-1. The social scale from a quality of life survey improved for those treated with amantadine for 12 months ($p=0.02$). Side effects included depression (1.3%), impotence (0.7%), and weight loss (0.7%).

In summary, oral amantadine therapy for hepatitis C is safe and effective compared to placebo and response rates are similar to interferon therapy alone but with fewer side effects. Amantadine may provide a safe alternative treatment for those unresponsive or intolerant to interferon, children, patients with depression/psychiatric history, patients with thrombocytopenia or leucopenia as well as transplant recipients.

Pegylated (40 kDa, Branched) Interferon Alfa-2a (PEG-IFN) and Ribavirin (RIBA) in IFN-naive Patients with Hepatitis C and Advanced Fibrosis/Cirrhosis: Interim Results of a Randomized, Controlled Trial

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PEG-IFN alone (180ug sc weekly for 48 wks) lead to sustained HCV-clearance in 26/87 (30%) patients (pts) with chronic hepatitis C and advanced fibrosis/cirrhosis (Heathcote et al. NEJM 343: 1673, 2000). Only a few pts with advanced fibrosis/cirrhosis were included in recent trials on pegylated interferons plus RIBA (Manns et al. Lancet 358: 958, 2001; Fried et al. Gastro 120 (suppl 1): A55, 2001). Thus, despite the high medical need for therapy, little is known on efficacy and tolerability of PEG-IFN and RIBA in pts with advanced HCV-associated fibrosis/cirrhosis.

The aim of this study is to compare efficacy and tolerability of PEG-IFN (180ug sc weekly) and RIBA (1000/1200 mg vs. 600/800 mg po QD) in treatment-naive pts with HCV-associated advanced fibrosis/cirrhosis. This trial is an open-label, randomized, controlled, trial in 11 Swiss centers. Inclusion criteria included naive pts (both genders, 18-70 yrs old) with HCV-associated biopsy-proven (≤ 12 months) advanced fibrosis/cirrhosis (Metavir F3-F4) and < 8 Child-Pugh points, elevated ALT and positive HCV-RNA in serum (Amplicor® HCV Monitor™). Randomization (1:1) stratified according to genotype (2/3 vs. other; Inno-Lipa®) to PEG-IFN (180ug sc once weekly) and either RIBA (≤ 75 kg: 1000mg, > 75 kg: 1200mg po QD) or (≤ 75 kg: 600mg, > 75 kg: 800mg po QD) for 48 wks with 24 wks of follow-up. Primary endpoint: sustained virologic response, secondary endpoints: initial (24 wks of treatment) and end-of-treatment virologic responses, tolerability.

So far, 88 pts enrolled (40 (45%) females; 30 (45%) genotype 2/3, 40 (45%) genotype 1). 43 pts randomized to higher, 45 pts to lower RIBA dose. Interim analysis at 24 wks of treatment: HCV-RNA in serum negative (< 1000 cps/ml) after 2, 4, 8, 12 and 24 wks of treatment in 24/71 (34%), 36/65 (55%), 43/63 (68%), 37/53 (70%) and 25/28 (89%) pts, respectively, with no difference between treatment arms. Treatment prematurely terminated in 5 (6%) pts for AEs, of which two were severe (attempted suicide, incidental PEG-IFN over-dose); dose reduction was necessary in 38 (43%) pts with no difference between treatment arms.

In summary, 24 wks of PEG-IFN+RIBA has resulted in negative serum HCV-RNA in almost 90% of pts with advanced HCV-associated fibrosis/cirrhosis and is acceptably tolerated. In which proportion this high initial response rate translates into sustained HCV clearance remains to be seen. What is very interesting so far in this study is that even though there appears to be a trend towards improved results with the higher doses of ribavirin (1000/1200mg/day versus 600/800mg/day) it has not reached statistical significance.