

# HCV Treatment Plenary Session



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## Interferon-Alfa2b in Combination with Ribavirin for the Treatment of Chronic Hepatitis C in Children – abstract 691

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Chronic hepatitis C is usually asymptomatic in children but significant liver disease, including cirrhosis, may occur. Approximately 40% of adults with chronic hepatitis C treated with interferon-alfa2b in combination with ribavirin become persistently HCV RNA negative. However, little is known about the efficacy and safety of this combination therapy in children with chronic hepatitis C.

The aim of this study was to determine the efficacy and safety of interferon-alfa2b in combination with ribavirin in children with chronic hepatitis C.

We enrolled 70 children with chronic hepatitis C from 17 centers worldwide: median age 10.5 yrs (range 3-16 yrs); White 56, Hispanic 8, Asian 3, African-American 2, Other 1; Male: Female 34:36; mode of acquisition was vertical (n=43), transfusion (n=25) and unknown (n=2); median duration of infection 10.4 yrs; mean baseline ALT 52 U/L (range 20-108 U/L) and HCV RNA level 1.5 million copies/ml; HCV genotype 1 (n=52), type 2 (n=9), type 3 (n=8), type 4 (n=1).

Ribavirin was given as syrup (n=55) or in capsules (n=15). All children received interferon-alfa2b (3MU/m<sup>2</sup> tiw) plus ribavirin (15 mg/kg/d, max 1200 mg/d), based on clinically derived pharmacokinetic data (*Kelly D.A et al Safety, efficacy and pharmacokinetics of interferon alfa2b plus ribavirin in children with chronic hepatitis. Hepatology 2001,34:A680*).

Children who had undetectable serum HCV RNA (<100 copies/ml) or >2 log decrease in viremia at treatment week 24 completed 48 weeks of therapy; treatment was discontinued in all others. A sustained virologic response was defined as undetectable HCV RNA (<100 copies/ml) 24 weeks after completion of therapy.

Based on intent-to-treat, 34/70 (49%) of all treated children had a sustained virologic response. A sustained virologic response occurred in 29/43 (67%) of children who received 80% of the interferon-alfa2b and ribavirin doses and completed at least 38 weeks of treatment and in 5/27 (19%) who did not (p<0.001). A sustained virologic response was more common in children <12 yrs old (57% vs 30% for >12 yrs, p=0.04) and in those infected with HCV type 2/3 (82% vs 38% for HCV type 1, p=0.002). HCV RNA levels <2 million copies/ml was associated with improved sustained virologic response rates in children infected with HCV type 1 (53% vs 18% for HCV RNA >2 million copies/ml, p=0.02) but not in those infected with HCV type 2/3. The rate of sustained virologic response was not associated with ethnicity, gender, mode of acquisition, estimated duration of infection, baseline ALT or ribavirin formulation.

Adverse events included fever (n=48), headache (n=45), fatigue (n=36), influenza-like symptoms (n=9), anorexia (n=38), weight loss (n=22) and depression (n=9). During treatment, anemia occurred in 10/70 (14%), neutropenia (ANC <1000 cells/mm<sup>3</sup>) in 19/70 (27%) and thrombocytopenia (platelet count <100K/mm<sup>3</sup>) in 1/70 (1%). Adverse events due to either neutropenia, anemia or depression led to dose

modification in 14/70 (20%) and discontinuation in 5/70 (7%) of the treated children.

In summary:

- ◆ Interferon-alfa2b in combination with ribavirin is effective and safe in children with chronic hepatitis C
- ◆ Factors associated with a favorable sustained virologic response in children include treatment duration, younger age, infection with HCV type 2/3, and lower HCV RNA level for those infected with HCV type 1.

Additional Points:

- ◆ There clearly was a decrease in both the height and weight parameters during treatment. The weight had almost returned to baseline at the end of therapy – the height takes longer to resolve. There are ongoing studies to show the significance of this 5 years post treatment. Additionally there is also on-going research looking at learning impairment during treatment.
- ◆ This study used extremely high doses of ribavirin when compared to the tolerated adult dosages of ribavirin. It is believed that children are able to tolerate these doses without sequel – only 2 cases of anemia in this study.

### **Improved Medication Adherence with Cognitive Behavioral Therapy in Patients Receiving Pegylated Interferon Alpha 2b (1.5 mcg/kg Wk) Plus Ribavirin (800-1400 mg/d): Results of a Prospective, Randomized, Controlled, Multi --abstract 592**

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PEG-Interferon alpha 2b 1.5 mcg/kg/wk + ribavirin 800 mg/d is effective for patients with chronic hepatitis C virus (HCV) infection. Increased medication adherence to interferon alpha 2b + ribavirin significantly increases SR. There is anecdotal evidence that the adherence rate in the community where most patients with HCV are treated is poor with high medication drop out and dose reduction rates. Thus, there is impetus to develop techniques to improve medication adherence for patients treated in community practice.

We sought to determine the feasibility and efficacy of AI utilizing patient education, aggressive side effect management and expanded supportive nursing intervention with cognitive behavioral therapy by telephone in patients with HCV treated with PEG- Interferon alpha 2b + ribavirin.

Patients with chronic HCV (+ HCV RNA) for whom medical therapy was planned were eligible. 10 gastroenterology/hepatology groups were selected for participation. 5 groups were randomized to the Active Intervention (**AI**) arm and 5 groups were randomized to standard of care (**SC**) for that group. Up to 10 patients were to be enrolled by each group such that up to 50 patients would receive **AI** and up to 50 patients would receive SC. Patients enrolled prior to receiving PEG-Interferon alpha 1.5 mcg/kg/wk + ribavirin (800-1400 mg/d) for 48 weeks. The **AI** arm consisted of the following: Experienced nurses who help patients with HCV on medical therapy by telephone in the Be-In-Charge Program were taught behavioral therapy techniques by an experienced therapist. Patients in the **AI** arm were to call these nurses on 6 defined occasions from just prior to beginning medical therapy until week 12 of therapy. Aggressive

medication side effect management was undertaken. Patients in the **SC** arm received routine supportive care used by their physician. SR rates, adverse event profiles, and quality of life measurements (SF 36) were determined in both groups. Preliminary 12-week drop out rates and quality of life measurement results are reported.

The 5 groups randomized to the **SC** (standard of care) arm enrolled 39 patients. 1 group randomized to the **AI** (active intervention) group did not recruit patients and was eliminated from the study. The other 4 groups randomized to the **AI** group enrolled 38 patients.

4/39 (10%) in the **SC** arm discontinued therapy within the first 12 weeks, compared with 1/38 (3%) in the **AI** arm. Dose modification of PEG-Interferon alpha were similar in the two groups (5/39 (13%) **SC** vs. 7/38 (18%) **AI**). Regarding health related quality of life, **AI** reduced the treatment impact on all domains of SF-36, except Bodily Pain and Mental Health. The magnitudes of alleviation by **AI** as compared to the **SC** at therapy weeks 4 and 8 were 51%/54% for Physical Functioning, 25%/36% in Role Physical, 81%/78% for General Health, 29%/55% in Vitality, 35%/50% in Social Functioning, and 48%/85% in Role Emotional. Based on the Physical and Mental summary scores, **AI** provided improvements at therapy week 4 and 8 from the **SC** by 32%/38% in physical-related HRQL and 44%/82% in mental-related HRQL.

In summary:

- ◆ **AI** utilizing patient education, aggressive side-effect management and nursing support by telephone, using cognitive behavioral therapy yields a decrease in drop-out rate in the first 24 weeks of medical therapy for HCV.
- ◆ **AI** results in significant improvements in physical-related and mental health-related quality of life at weeks 4 and 8 (of medical therapy for HCV).
- ◆ Telephone nursing support, utilizing cognitive behavioral therapy is feasible and can be performed on a large scale basis. This study was supported with a grant from Integrated Therapeutics, Inc., a subsidiary of Schering Plough, Inc.

Additional Points:

- ◆ 3 patients in the **AI** arm needed growth factors however the researcher did not feel that the usage impacted results.
- ◆ The HCVRNA 24 week data was the same in both groups.
- ◆ The phone calls were done on a “group basis” with about 6 people on each call. The average call was approximately 30 minutes.

### **Sustained Antiviral Response with Consensus Interferon (CIFN) Plus Ribavirin or Interferon Alfa-2b (INF Alfa-2b) Plus Ribavirin in Treatment Naïve Subjects with Chronic Hepatitis C. A Pilot Study—abstract 593**

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We conducted a prospective randomized clinical trial to observe if treating naive subjects with chronic hepatitis C with CIFN and ribavirin was safe and effective when compared to treatment with IFN alfa-2b and ribavirin.

Group 1 received 3MU IFN alfa 2b three times a week. Group 2 received 15 mcg CIFN three times a week. All volunteers received 1-gram ribavirin/day. The study group consisted of 127 subjects, 64 in-group 1 and 63 in-group 2. The medications were given for 24 weeks. If HCV RNA was undetectable at week 24, the

subjects were continued on treatment for 48 weeks, otherwise treatment was discontinued. Sustained antiviral response (negative HCV RNA at week 72) was the primary end point. Subjects in the two groups were similar in gender (68% for both groups), age (mean age: 43 years for both groups), ethnic background (62% and 68% Caucasians, respectively), HCV genotype 1 (75% and 65%, respectively), initial HCV RNA titer (mean 3.8 and 4.9 million copies, respectively) and liver histology (25% cirrhosis).

The combination of CIFN and ribavirin resulted in a significantly higher sustained viral clearance than the combination of IFN alfa 2b and ribavirin, particularly in genotype-1 infected subjects.

Sustained Virological Response:

- ◆ Overall SVR CIFN/RBV was 57% versus 39% for IFN/RBV.
- ◆ Overall SVR CIFN/RBV for genotype 1 was 44% versus 26% for IFN/RBV.
- ◆ The overall SVR for Genotype 1 HVL was 46% for CIFN/RBV versus 11% for IFN/RBV p=0.007 (four fold increase for CIFN versus IFN/RBV).
- ◆ The overall SVR for Genotype 1 LVL was 39% for CIFN versus 45% for IFN/RBV.
- ◆ The overall SVR for genotype 2/3 was 82% for CIFN/RBV versus 77% for IFN/RBV.

In summary, given the greater representation of non-Caucasians in this study when compared to previous trials, the sustained antiviral response rate of the combination of CIFN plus ribavirin is competitive to that reported for the pegylated interferons plus ribavirin and could be considered as an alternative treatment, especially in patients infected with genotype 1.

Additional Points:

- ◆ Although the percentage of Caucasians was fairly equal in both groups, there was almost double the amount of African Americans in the Rebetrone group than the Consensus IFN/RBV group. This potentially could have significantly impacted the results in favor of Consensus IFN/RBV

## **A Prospective Randomized 24 Week Trial of Peg-Interferon Alpha 2b Plus Ribavirin Versus Standard Combination Therapy in Untreated Hepatitis C Genotype 2 and 3 Patients – abstract 59**

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Recent clinical studies demonstrated, that combination treatment of standard interferon with ribavirin is as effective as a combination of pegylated interferon with ribavirin in hepatitis C genotype 2 and 3 patients. The studies were not designed to evaluate the primary efficacy of the therapies for genotype 2 and 3 patients and furthermore treatment was conducted for 48 weeks.

The aim of the present study was to investigate prospectively in untreated hepatitis C patients with genotype 2 and 3 the effect of a 24 week treatment with pegylated interferon alpha 2b and ribavirin in comparison with standard interferon and ribavirin therapy.

Between August 2000 and September 2001, 72 previously untreated patients with hepatitis C genotype 2 and 3 of the universities of Hamburg and Kiel were enrolled. Patients were assigned to either a therapy with standard interferon alpha 2b 3 MU 3 times weekly in combination with ribavirin 1000-1200mg per day for 24 weeks (n = 36) or the combination of pegylated interferon alpha 2b 100 microgram weekly with low dose ribavirin 800mg daily for 24 weeks (n= 36).

Sustained response (SR) and end of treatment response (ETR) were measured by HCV-RNA determination by PCR (Roche Cobas Amplicor) with a detection limit of 50 IU/ml.

Furthermore quality of life was assessed by the SF 36 questionnaire. The mean age of the patients was 33 years (41 male and 31 female). All patients reached end of treatment (ETR) with 2 drop outs (2,9%), thus 70 patients are evaluable. Weight 67.6 and 69.3kg for the standard IFN and Peg Group respectively

Results are presented as intend to treat results.

**SVR (83.3) 77.7 NS Peg Group and standard group respectively:**

<60kg -	85.7% standard versus 100% Peg
60kg – 80kg	80.9% standard versus 88% Peg
>80kg	62.5% standard versus 57.1% Peg

There was no difference in quality of life during the entire treatment measured by the SF 36 questionnaire. For previously untreated hepatitis C genotype 2 and 3 patients, a 24 week treatment schedule achieves comparable results as obtained in the large 48 week trials. For genotype 2 and 3 patients, pegylation of the interferon does not effect the treatment outcome or the quality of life during the 24 week therapy

**Comparison of Therapy with PEG-Intron 0.5 Mcg/kg Versus Colchicine 0.3 Mg BID in 250 Patients with Cirrhosis and HCV; Interim Data from COPILOT—abstract 595**

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COPILOT is a study comparing maintenance PEG-Intron 0.5mcg/kg to colchicine 0.6mg bid (twice daily) in patients who have failed prior interferon therapy with HCV and advanced fibrosis. The 1 year safety data was presented at DDW 2002 and we are now presenting interim efficacy data on patients with cirrhosis (Ishak 5 or 6) who have completed at least 1 year of therapy.

Patients were randomized to colchicine (122) or PEG-Intron (128). Groups were well matched for gender (72% colchicine, 74% Peg Intron male); age (mean 49yrs – both groups), duration of disease (60% > 20 years); ethnicity (13%, 14% AA); CPT score were well matched; genotype 1 (90%, 84%); genotype 2 (5%, 8%), genotype 3 (5%, 8%)viral load (64% > 850,000 iu, Roche Amplicor). All patients had received prior Intron, Rebetron or PEG-Intron plus ribavirin therapy and were non-responders to at least 3 months of treatment with 50% having had more than one course of treatment.

Data at one year is given for ALT, HCV RNA, AFP and clinical outcomes. ALT fell in colchicine group from 112 iu to 70 iu and on PEG from 87 to 47iu; p= ns for both groups. AFP did not change over 1 year in either group. Viral load fell by 1 log in 90% of patients on PEG-Intron, p=0.06 but did not change in colchicine patients. Clinical outcome were seen in 10 patients in the colchicine group and included the following: liver transplant 3 patients, increase in CPT > 2 points over baseline that was sustained in 3 patients; variceal bleed 3 patients; and HCC 1 patient. In the PEG-Intron group 1 patient developed progressive liver failure and died. One patient died in a MVA. Two patients were found to have HCC within 4 weeks of randomization and on review HCC was found in the baseline screening US or CT scan and these patients should have been excluded by study protocol but are included on ITT analysis. Adverse events were 2 for colchicine and 4 for PEG-Intron.

In summary, preliminary 1 year data from COPILOT shows viral load reduction on PEG-Intron but not colchicine. 8% of patients on colchicine in year 1 have had a clinical endpoint reached compared to 3% on

PEG-intron. However, only 1 true liver related endpoint has been seen in PEG-Intron group. A second analysis will be due at 2 years to see if the clinical outcomes trend continues in favor of PEG-Intron.

Additional Points:

- ◆ Safety of 0.5 mcg Peg Intron is excellent
- ◆ Pegylated interferon reduces ALT in treatment
- ◆ Trend shows a reduction in HCC in the pegylated interferon group

## **Peginterferon Alfa-2a (40KD) (PEGASYS®) in Liver Transplant Recipients with Established Recurrent Hepatitis C: Interim Results of an Ongoing Randomized Multicenter Trial – abstract 596**

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Hepatitis C virus (HCV) infection is the leading cause of cirrhosis and hepatic failure that leads to orthotopic liver transplantation (OLT). Recurrent infection with HCV is a significant cause of allograft dysfunction and of progression to end-stage liver disease and allograft failure after OLT. The effectiveness of standard interferon (IFN) in patients with established recurrent HCV post-OLT has not been satisfactory. Higher sustained virological response (SVR) rates have been demonstrated with IFN and ribavirin (RBV) combination therapy; however, RBV is often not well tolerated in liver transplant recipients.

The objective of this study was to investigate the safety and efficacy of peginterferon alfa-2a (40KD) (PEG-IFN a-2a [40KD]) in patients with established recurrent HCV post-OLT.

Previously untreated HCV-infected post-OLT recipients who were transplanted between 6 and 60 months prior to study initiation were randomized in a 1:1 ratio to:

- ◆ Peginterferon alfa-2a (40KD) (PEG-IFN  $\alpha$ -2a [40KD]) 180 $\mu$ g once-weekly (n=33) or untreated (n=32).
- ◆ Patients were stratified according to viral load: HCV RNA  $\leq 1 \times 10^6$  IU/mL [low] vs  $> 1 \times 10^6$  IU/mL [high].
- ◆ Treatment was for 48 weeks, with an additional 24 weeks of treatment-free follow-up.
- ◆ A positive response to therapy was defined as undetectable HCV RNA (COBAS AMPLICOR® HCV Test, v.2.0, with lower limit of detection  $<50$  IU/mL). A  $2\text{-log}_{10}$  drop in HCV RNA (COBAS AMPLICOR HCV MONITOR® Test, v2.0, with lower limit of detection  $<600$  IU/mL) compared with baseline was used as a predictor of virological response. SVR was defined as HCV RNA  $<50$  IU/mL at 24 weeks following the end of therapy.

To date, 65 patients have been randomized into the study. Study enrollment has been completed, and baseline characteristics of the patients were as follows: peginterferon alfa-2a (40KD): mean age  $52.7 \pm 7.87$  years, 76% male, 82% high viral load, and 79% HCV genotype 1; Untreated: mean age  $50.7 \pm 6.54$  years, 81% male, 84% high viral load, and 75% HCV genotype 1. Sixty-five, 65, 64, and 46 patients have had HCV RNA evaluations at 4, 12, 24, and 48 weeks of the study, respectively.

The response to therapy is summarized below:

Group	Week 4		Week 12		Week 24		Week 48	
	HCV	HCV	HCV RNA	HCV RNA	HCV RNA	HCV RNA	HCV RNA	HCV RNA

	<b>RNA Neg.</b>	<b>RNA 2-Log Drop</b>	<b>Neg.</b>	<b>2-Log Drop</b>	<b>Neg.</b>	<b>2-Log Drop</b>	<b>Neg.</b>	<b>2-Log Drop</b>
PEG-IFN $\alpha$ -2a (40KD)	4/33 (12%)	12/33 (36%)	11/33 (33%)	15/33 (45%)	10/32 (31%)	16/32 (50%)	8/23 (35%)	11/23 (48%)
<b>Untreated</b>	0/32 (0%)	0/32 (0%)	0/32 (0%)	0/32 (0%)	0/32 (0%)	0/32 (0%)	0/23 (0%)	0/23 (0%)

Four rejection episodes have been observed to date in the peginterferon alfa-2a (40KD) arm of the study; 3 patients had a biopsy-proven rejection and 1 patient had a presumptive acute rejection. One patient with the biopsy-proven reaction withdrew from the study due to thrombocytopenia; 1 patient withdrew due to acute rejection; the third patient completed the trial. The patient with the presumptive acute rejection completed the trial. Ten patients randomized to the peginterferon alfa-2a (40KD) arm and 6 patients randomized to the untreated arm have been discontinued from the trial. Two of the 10 discontinued patients from the peginterferon alfa-2a (40KD) arm discontinued during the treatment-free follow-up phase. There were 2 deaths found unrelated to peginterferon alfa-2a (40KD) at day 82 and day 484 due to hepatic and renal failure and due to pulmonary metastases, respectively. Fifteen patients (45%) randomized to the peginterferon alfa-2a (40KD) arm experienced at least 1 serious adverse event. Eight patients (25%) randomized to the untreated arm experienced at least 1 serious adverse event.

In summary, these findings reveal a significant antiviral effect for peginterferon alfa-2a (40KD) in patients with established recurrent HCV post-OLT. Overall, peginterferon alfa-2a (40KD) treatment has been well tolerated.