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**HEPATIC GENE EXPRESSION PROFILES DURING TREATMENT WITH PEGINTERFERON AND RIBAVIRIN: IDENTIFYING IMPORTANT MOLECULAR PATHWAYS FOR TREATMENT RESPONSE** Jordan J. Feld<sup>1</sup>, Santosh Nanda<sup>1</sup>, Pusek Susan<sup>2</sup>, Lisa Schweigler<sup>2</sup>, Dickens Theodore<sup>2</sup>, Karen Dougherty<sup>2</sup>, Steven Zacks<sup>2</sup>, Roshan Shrestha<sup>2</sup>, T Jake Liang<sup>1</sup>, Michael Fried<sup>2</sup>;

<sup>1</sup>NIDDK, NIH, Liver Diseases Branch, Bethesda, MD, MD;

<sup>2</sup>University of North Carolina, Chapel Hill, NC

**Background:** The reasons for hepatitis C treatment failure remain unknown but may relate to different host responses to therapy. **Aim:** To compare hepatic gene expression in patients prior to and during peginterferon and ribavirin therapy, and to evaluate the effect of pretreatment with ribavirin on peginterferon-induced hepatic gene expression. **Methods:** The treatment group received therapy prior to liver biopsy: 5 patients received peginterferon alfa-2a alone 24 hours prior to biopsy (PEG) and 6 patients received ribavirin for 72 hours then peginterferon alfa-2a 24 hours prior to biopsy (PEG+RBV). Treated patients were divided by response: rapid responders (RR)>2 log drop in HCV RNA by week 2 (n=6) and slow responders (SR)<2 log drop in HCV RNA by week 2 (n=5). Pretreatment biopsy specimens were obtained from a control group matched for gender, race, viral load, genotype and histological disease. Controls were grouped as SVR or NR based on subsequent treatment response. After RNA extraction, gene expression profiling was performed using standard Affymetrix microarray technology (54,000 gene platform - full human genome). Expression differences of 1.5 fold with a p-value<0.01 were considered significant. **Results:** Eleven patients in the treatment group were compared to 19 in the control group. 1274 genes differed between treatment and control groups. Known ISGs and genes involved in the immune response were induced in treated patients. 563 genes differed between patients that received PEG+RBV and those receiving PEG alone prior to liver biopsy. Patients pretreated with ribavirin had heightened induction of IFN-related genes, including the IFN- $\alpha$  receptor, and showed down-regulation of genes involved in IFN inhibition, apoptosis and hepatic stellate cell (HSC) activation. Examining treatment response, 1064 genes differed between RR and SR patients. IFN inhibitory pathways and genes involved in HSC activation and apoptosis were down-regulated in RR patients. In the control group, NRs had higher expression of numerous ISGs than SVRs. **Conclusion:** Induction of interferon inhibitory pathways may account for reduced treatment efficacy as seen in the slow responder group. Patients achieving a rapid decline in viral load and those treated with peginterferon plus ribavirin showed similar expression patterns with down-regulation of genes involved in apoptosis, HSC activation and interferon inhibition. Ribavirin may also provide synergy to interferon through up-regulation of the interferon receptor. Collectively these mechanisms may provide a molecular basis for the improved efficacy of combination therapy.

**Disclosures:**

The following people have nothing to disclose: Jordan J. Feld, Santosh Nanda, Pusek Susan, Lisa Schweigler, Dickens Theodore, Karen Dougherty, Steven Zacks, Roshan Shrestha, T Jake Liang, Michael Fried

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**CLINICAL, BIOCHEMICAL, VIROLOGIC AND HISTOLOGIC OUTCOMES OF CHRONIC HEPATITIS C FOLLOWING SUSTAINED VIROLOGIC RESPONSE (SVR) TO HCV THERAPY: A PROSPECTIVE 5 YEAR COHORT STUDY** Adrian M. Di Bisceglie, Sarah L. George, Kusal L. Mihindukulasuriya, Joyce Hoffmann, Bruce R. Bacon; Internal Medicine, Saint Louis University, St. Louis, MO

**Background:** Little is known about long-term outcomes in chronic hepatitis C following SVR. We determined the 5 year clinical, biochemical, virologic, and histologic outcome in 150 adults with chronic hepatitis C achieving SVR following antiviral therapy. **Methods:** Patients with SVR were enrolled 6 to 12 mos after completion of therapy. Subjects were seen initially and then annually to monitor clinical outcome, serum aminotransferases and HCV RNA. Those with initial stage >2 fibrosis were re-biopsied in

year 4 or 5; data on other follow-up liver biopsies was also collected. Serum HCV RNA was assessed by PCR at every visit and by Transcription-Mediated Amplification (TMA, Bayer) on the latest available sample. The grade and stage of hepatitis C were assessed using the Scheuer scoring system. **Results:** 76 patients (50%) were female, 148 were Caucasian (98%) and their mean age at entry was 49 years. Initial HCV genotypes were 1 (53%), 2 (34%), 3 (10%), 4 (2%) and unknown (6%). 86% received standard interferon alfa-2b with ribavirin, 4% pegylated interferon and ribavirin while treatment for the remainder was not recorded. 115 patients (77%) have been followed for at least 4 years. During this time, 2 developed HCC requiring OLT (both were cirrhotic) and another died of unknown causes. No other liver-related clinical outcomes were noted. Only 1 patient had transiently detectable HCV RNA by PCR, not accompanied by a rise in ALT. Serum from 8 of 146 patients (5.4%) was repeatedly reactive for HCV RNA by TMA a mean of 4 years after completion of treatment; serum ALT was normal in all 8 (mean 22, range 11-28). Among 40 subjects with pre-treatment liver biopsies available for review who underwent repeat liver biopsy, both the mean stage (2.3 vs 1.2, p<0.001) and mean grade (2.6 vs 1.5, p<0.001) of hepatitis improved significantly. The stage of fibrosis among 34 patients with stage 2 or greater improved in 27 (79%), remained unchanged in 7 (21%) and worsened in none (see table). Paired biopsies were available from 2 of the 8 TMA-positive patients. The grade and stage improved substantially in one (from G 3, S 4 initially to G 1, S 1) while in the other it was unchanged (G 2, S 1). **Conclusions:** Individuals with chronic hepatitis C who achieve SVR are at very low risk for virologic relapse, have continued improvement of liver histology over 5 years but may remain at risk of HCC if cirrhosis persists.

Stage Pre	No.	Stage of Fibrosis Post			
		4	3	2	1
4	7	2	2	1	2
3	14	0	1	3	10
2	13	0	0	4	9

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**PEGYLATED INTERFERON ALFA 2 B + RIBAVIRIN ARE EQUALLY EFFICACIOUS AND WELL TOLERATED IN PATIENTS >65 YEARS OLD IN COMPARISON TO OTHER AGE GROUPS: SUBANALYSIS OF A RANDOMIZED, CONTROLLED STUDY (WIN-R TRIAL)** Steven L. Flamm<sup>1</sup>, Ira M. Jacobson<sup>2</sup>, Robert Brown<sup>3</sup>, Bradley Freilich<sup>4</sup>, Nezam Afzhal<sup>5</sup>, Paul Kwo<sup>6</sup>, John Santoro<sup>7</sup>, Scott Becker<sup>8</sup>, Adil Wakil<sup>9</sup>, David Pound<sup>10</sup>, Joanne Harvey<sup>11</sup>, Louis H. Griffel<sup>11</sup>, Clifford A. Brass<sup>11</sup>; <sup>1</sup>Northwestern University, Chicago, IL; <sup>2</sup>Weill Medical College of Cornell University, New York, NY; <sup>3</sup>Columbia University College of Medicine, New York, NY; <sup>4</sup>Baptist Medical Center, Kansas city, MO; <sup>5</sup>Beth Israel Deaconess Medical Center, Boston, MA; <sup>6</sup>Indiana University School of Medicine, Indianapolis, IN; <sup>7</sup>Atlantic Gastroenterology, Egg Harbor Township, NJ; <sup>8</sup>Austin Gastroenterology, PA, Austin, TX; <sup>9</sup>California Pacific Medical Center, San Francisco, CA; <sup>10</sup>Indianapolis Gastroenterology, RSCH, Indianapolis, IN; <sup>11</sup>Schering Plough Research Institute, Kenilworth, NJ

**Background:** Peg interferon  $\alpha$  (IFN) + ribavirin are the standard of care for chronic HCV. There is reluctance to administer anti-viral medications to older populations due to a fear of side effects and possible decreased efficacy. Limited data is available on pts. age >65 due to ineligibility for clinical trials. The role of age in determining response to IFN-based anti-viral therapy for chronic HCV has not been clearly defined. **Aim:** To determine if age is an independent predictor of sustained virological response (SVR) or medication tolerability within a randomized, controlled clinical trial of treatment-naïve pts. with HCV. Patient age grps studied: 18-25 yrs., n=69; 26-35 yrs., n=350; 36-45 yrs., n=1866; 46-55 yrs., n=2200; 56-65 yrs., n=368; and >65 yrs., n=55. **Methods:** A retrospective review of the multi-center WIN-R trial database was undertaken. Pts. were randomized to receive PEG IFN $\alpha$  2b (1.5 $\mu$ g/