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24 Hour Load Decline as Predictor of Treatment Outcome in Chronic Hepatitis C Virus Genotype 4 Infection

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Primary IFN-resistance as defined by a decline in viral load of less than 0.5 log 24h after 5 MU IFN alfa is a predictor of outcome of IFN/ribavirin therapy in chronic HCV genotype 1 infection.

The aim of this study was to investigate this test in patients with genotype 4. Treatment-naive pts with biopsy-proven chronic hepatitis C due to genotype 4 were studied. At day -21 pts received 10MU IFN alfa2b once. One week later treatment with 5MU IFN/d for the following 2 weeks (days -14 to -1) was given. Thereafter (day 0) therapy with 5MU IFN/2d or 1.5microg/kg PEG-IFN alfa2b weekly and 1000-1200mg ribavirin/d was initiated. Viral load was determined using the Cobas Amplicor Monitor HCV Assay v2.0 before and 24h after 10MU (days -21 and -20), before and after the first 5MU dose (days -14 and -13), and on days -7 and -1.

Currently 10 pts (median age: 40 years; range 34-50; male: female = 6:4) have completed the study phase, 6 of them became month 3 responders (R). Baseline ALT was 60.5 IU/L (14-190; normal range 0-23 IU/L). 3 pts had liver cirrhosis. The median baseline viral load was 278500 (range:16400-539000) and 252500 IU/mL (18500-603000; p=0.58) on days -21 and -14, respectively, and was not different between R and nonresponders (NR). 24h after 10 and 5 MU IFN viral load decreased by 1.40 log (range 0.27-1.91) and 0.95 (0.13-1.77; p=0.028), respectively. The decrease 24 hours after 5 MU IFN log change was higher in R (1.28; 0.90-1.77) than in NR (0.40; 0.13-0.46; p=0.011). After 14 days of 5MU IFN/d it was 2.97 (2.20-3.41) in R and 0.40 (0.27-0.74; p=0.011) in NR, respectively. There was a close correlation between the decline after 24h and 14d on 5MU IFN/d (r=0.93; p=0.0001). A log change of 0.5 24h after 5 MU IFN was a useful cutoff value for prediction of treatment outcome (sensitivity and specificity 100%).

In summary, for genotype 4 the initial response to IFN is dose-dependent and there are primary IFN-resistant viral strains analogously to HCV genotype 1 infection. Viral decline 24h after a single test dose is a useful predictor of treatment outcome

A Pilot Study to Assess the Effect of Targeted COX-2 Inhibition on Liver Histology in Patients with Hepatitis C Virus (HCV)

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Hepatocellular carcinoma is one of the most common malignancies with a worldwide annual incidence exceeding one million. HCV infection is a known risk factor for cirrhosis and HCC. In the USA an estimated 500% increase in incidence of HCC is expected over the next 10 years due in large part to HCV. Preliminary data suggests that hepatic COX-2 is over-expressed in persons with viral hepatitis, cirrhosis and HCC.

The aim of our study is to determine if targeted COX-2 inhibition could potentially reduce hepatic inflammation in chronic HCV infection. We designed a pilot study to determine if targeted COX-2 inhibition for six months would result in histologic improvement and a decrease in hepatic COX-2 expression in patients with HCV. Patients chronically infected with HCV, naive to interferon therapy, and without fibrosis or HCC on liver biopsy, were eligible for enrollment. Following a baseline liver biopsy, each patient received celecoxib 200 mg orally twice daily for six months, after which a repeat liver biopsy was performed. A single blinded pathologist reviewed each specimen utilizing a modified Knodell scoring system.

Three patients to date have completed the study. Two patients demonstrated significant reduction in piecemeal necrosis and portal inflammation with no progression in fibrosis. The third patient had no change in inflammation but developed evidence of early bridging fibrosis at six months with a fibrosis score of 1/6 at enrollment and 2-3/6 at six months.

In summary, preliminary data from this pilot study was notable for histologic improvement in two out of three patients who completed six months of celecoxib therapy. A third patient had no change in inflammation but developed early fibrosis at six months. This study is ongoing and will eventually enroll up to 15 patients and include data regarding COX-2 expression using immunohistochemistry and quantitative PCR techniques. In patients with chronic HCV, targeted COX-2 inhibition may reduce hepatocellular inflammation and eventually slow the progression to cirrhosis and HCC. Promising results using targeted COX-2 inhibition could lead to a larger long-term study in patients with chronic HCV employing COX-inhibitory chemoprophylaxis for cirrhosis and HCC.

The Association of Hypoglycemia and Peg Interferon Therapy in Chronic Hepatitis C

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As drug delivery techniques become more sophisticated, clinicians face the challenge of understanding each new drug with regard to the benefits and risk to their patients. PEG-interferon (IFN) +ribavirin has been developed for HCV treatment and shown an improved sustained viral response. While treating HCV patients with PEG-IFN, we noticed some patients developed hypoglycemia (serum glucose <70mg/dl), which has not been reported in the past.

The aim of this study is to assess the association of hypoglycemia and PEG-IFN therapy in HCV compared to standard IFN treatment. A total of 124 HCV patients were evaluated. The study group consisted of 61 patients treated with PEG-IFN alpha-2b (PEG INTRON) + ribavirin and 63 with standard IFN alpha-2b + ribavirin controls matched for age, race, gender, HCV genotype and fibrosis. Treatment-related changes in blood glucose level in the two groups of patients were analyzed. Per standard criteria for combination therapy, all patients had blood glucose level between 70 to 115g/dl at the time of enrollment. Blood glucose was measured at baseline and at 12 weeks during treatment. Hypoglycemia was defined as blood glucose < 70 g/dl.

At 12 weeks, 5 patients (8%) treated with standard IFN alpha-2b+Ribavirin developed blood glucose less than 70g/dl (blood glucose: 52-63 g/dl) while 18 patients (30%) treated with PEG-IFN alpha-2b and ribavirin therapy had hypoglycemia (29-68 g/dl) [P < 0.05]. There was a significant decrease in blood glucose in patients treated with PEG-IFN alpha-2b and ribavirin at 12 weeks in compared with pre-treatment baseline (78 + 2.4 vs. 93 + 2.9 g/dl) [P < 0.001], while there was no significant difference in blood glucose in patients treated with standard IFN alpha-2b + ribavirin at 12 weeks compared to baseline (90+3.2 vs. 91+ 2.8 g/dl) [P = 0.86]. Age, Gender, race, ALT, HCV genotype and liver histology were not associated with changes in blood glucose.

In summary, this is the first study to show the association of hypoglycemia and PEG-IFN alpha-2b (PEG INTRON) therapy in HCV patients. There was a very high prevalence of hypoglycemia (30%) and a significantly lower blood glucose in HCV patients treated with PEG-IFN + ribavirin at 12 weeks compared to standard IFN + ribavirin. This may support previous findings suggesting that antiviral administration with

PEG-IFN alpha-2b significantly decreased insulin autoantibodies (Ismaeil, Hepatology; 2000 32: 369A). Further research is needed to evaluate the involved detail pathogenesis and clinical outcome due to this effect of PEG-IFN alpha-2b treatment.