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1. Abstract Number: 315

METABOLIC COFACTORS PLAY AN IMPORTANT ROLE IN FIBROSIS PROGRESSION IN INITIALLY MILD CHRONIC HCV

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The outcome of mild chronic hepatitis c is controversial. We have followed 108 patients (61 males, 47 females, mean age at diagnosis 42.1 years) with minimal fibrosis (F0-F1-Metavir) in the initial liver biopsy. All patients remained untreated and had a second histological assessment after 7 to 11 years (mean 8.3 years). Fibrosis progression was seen in 60 cases (33 to F2, 13 to F3 and 14 to F4-cirrhosis). Fibrosis progression was significantly associated with alcohol intake (p=0.01), non-alcoholic hepatic steatosis (p=0.01), hyperlipemia (p=0.04), overweight (p=0.050) and type 2 diabetes (p=0.05). Patients with at least one of these variables had a significantly higher risk of progression to F3 (16%) or to F4-cirrhosis (22%) compared to cases without any of them (F3 rate: 8%, F4-cirrhosis rate: 4%) while no difference was seen in the risk of progression to F2 (patients with at least one variable present: 29% had progression, patients with no variable present: 36% had progression). Among patients without metabolic cofactors, fibrosis progression was significantly associated with the ALT profile during follow-up, with a 3,4 relative risk of progression in patients with mean ALT >100 IU/L, and no relation with the HCV genotype or viremia levels. These results indicate that alcohol and metabolic cofactors leading to hepatic steatosis play an important role in fibrosis progression in initially mild chronic hepatitis C.

2. Abstract Number: 268

COMPARISON BETWEEN LEUKOCYTE INTERFERON ALPHA PLUS RIBAVIRIN AND R-ALPHA2B INTERFERON PLUS RIBAVIRIN FOR TREATMENT OF CHC IN NAIVE PATIENTS:A MULTICENTER RANDOMIZED ITALIAN STUDY

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The aim of this study was to assess the long term efficacy and the safety profile of the combination of ribavirin plus leukocyte alpha IFN or r-alpha-2b IFN in naive patients affected by CHC. We enrolled from September 1998 ,423 naive patients randomly assigned to receive leukocyte alpha IFN or r-alpha-2b IFN at the same dosage(3MU thrice weekly)plus ribavirin(1000-1200 mg/daily)for 24 weeks. Primary end-points of the study were the rate of sustained virological response, the histological improvement in responder patients and the safety of treatments. Sustained virological response was observed in 47% of patients treated with

leukocyte IFN and in 45% of patients treated with recombinant IFN. Histological improvement was demonstrated in 40% of responders to leukocyte IFN and in 42% of responders to recombinant IFN. In regards to the safety profile, the group of patients treated with leukocyte IFN had a reduced rate of adverse events, with a greater compliance rate (96% vs. 89%) and a significantly reduced frequency of discontinued treatments. In summary, both combination therapeutic regimens are effective in inducing a sustained virological response and a histological improvement in CHC naive patients. However the safety profile of leukocyte alpha IFN plus ribavirin is better than r-alpha-2b plus ribavirin

3. Abstract Number: 459

PREDICTION OF TREATMENT OUTCOME IN PATIENTS WITH CHRONIC HEPATITIS C: SIGNIFICANCE OF BASELINE PARAMETERS AND VIRAL DYNAMICS DURING THERAPY

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Treatment of chronic HCV-infection with (pegylated)-IFN alpha 2B and ribavirin is recommended for 24-48 weeks considering the presence of HCV RNA in serum at week 24 and different pretreatment predictors (age, sex, genotype, baseline viremia, and fibrosis). Due to the considerable side effects and high treatment costs, it is highly desirable to determine the treatment duration on the basis of validated predictive parameters and to stop treatment in virologic non-responders as early as possible. We investigated 355 patients treated with (pegylated)-IFN alpha 2B and ribavirin for baseline parameters and early prediction of virologic response by HCV RNA decline (bDNA3.0) at week 4 and 12 by univariate and multivariate logistic regression analyses. HCV genotype 2 or 3 and a low GGT in serum were the only predictors for sustained response in all patients ($p < 0.00001$). A low baseline viremia was predictive only in genotype 1,4,6-infected patients ($p = 0.008$) but not in genotype 2,3 ($p = 0.508$). A negative HCV RNA test at treatment week 4 and 12 was predictive for sustained response in 78 and 84% of patients only. A viral load at week 4 and 12 of > 400.000 IU/mL and > 25.000 IU/mL, respectively was 100% predictive for virologic non-response (45% of nonresponders). In conclusions, from the current known pretreatment predictors of sustained response only HCV genotype was confirmed. Baseline viremia was predictive in HCV genotype 1,4,6-infected patients only. By measurement of HCV-viremia at week 4 and 12 virologic non-response can be predicted early in 45% of patients previously identified as non-responders at week 24.

4. Abstract Number: 5349

VITAMIN E DOESN'T REDUCE RIBAVIRIN ASSOCIATED ANAEMIA DURING COMBINATION THERAPY FOR HEPATITIS C

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Ribavirin causes dose-related hemolytic anemia and may reduce adherence to combination therapy in hepatitis C. Since ribavirin might induce oxidative stress of erythrocyte membrane, we have analysed the effect of Vitamin E supplementation during treatment. Among 43 patients with chronic hepatitis C treated with standard interferon-ribavirin combination, 21 received Vitamin E (200 mg daily) (group A) while 22 did not (group B). At baseline, the 2 groups were similar for body weight (72.1 vs. 73.9 Kg), Hb levels (145.09 gram/L vs. 145.7 gram/L). Patients were initially given 800-1000-1200 mg/daily of ribavirin according to body weight and were treated for 6-12 months according to HCV genotype. The effect of vitamin E was assessed comparing adherence to the assigned dose of ribavirin and drop in Hb levels (vs. baseline) seen during the

treatment period. Adherence to treatment was similar in the two groups according to mean daily ribavirin dose (group A: 919 mg corresponding to 12.75 mg/Kg; group B: 933 mg or 12,62 mg/Kg, p: ns) . Mean peak Hb drop was also similar (group A: 25+/-8.37 g/L, group B: 27+/-11 g/L p:ns). The Hb drop was >30g/L in 23% of group A and in 45% of group B (p=0.3). These results indicate that low dose Vitamin E supplementation doesn't protect from ribavirin-associated anemia during combination therapy for chronic hepatitis C.

5. Abstract Number: 456

HEPATITIS C VIRUS RNA IN PATIENTS WITH HIV INFECTION

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HIV infected patients who are anti-HCV reactive have a higher likelihood of testing positive for HCV RNA than patients with anti-HCV only. In addition, coinfecting patients have higher viral loads (J AIDS 2001;26:340-344). Little is known about: a) HIV patients who are anti-HCV positive/HCV RNA negative when evaluated, and b) the course of HCV viremia in those who are HCV RNA-positive.

The aim of this study was to assess demographic and laboratory variables associated with HCV RNA negativity in anti-HCV-positive HIV patients. 2. To evaluate variation in HCV RNA levels over time. We tested for HCV RNA in our cohort of anti-HCV positive HIV patients (N=229). In a subgroup of compliant HCV RNA positive patients, sera were prospectively collected and stored at -70C. The Roche MonitorTM assay was used to quantify HCV RNA, expressed in log₁₀ /mL (BH). CD4 counts were drawn within three months of the date of stored sera and measured in the Los Angeles County Central laboratory. Either Amplicor or an in-house qualitative RT-PCR tested the remainder of the cohort. The results showed that 13% of 177 HIV-infected patients were HCV RNA-negative when first evaluated. These 23 patients had lower CD4 counts, lower AST and ALT levels, were more likely to be Latinos (as opposed to Caucasian or Black) and less likely to have used injection drugs. By regression analysis, only Latinos (HR=3.5, 95% CI 1.2-10.8, p=0.03) and lower AST level (68 vs. 124 IU/L, p=0.02) were associated with HCV RNA-negativity. 38 patients (male:female 31:7) had at least 2 stored serum samples, collected at least 3 months apart. The follow-up ranged from 3.5 to 63 months (median 14). The median baseline HCV RNA was 6.47 log copies/mL. There was no statistical difference between the 14 patients with CD4 levels <200/ μ L (6.19 log copies/ml) vs. 24 patients with CD4 counts >200 (6.54 logs). The HCV RNA was plotted over time and compared to changes in CD4 counts. HCV RNA levels varied only an average of about 0.5 log over time. On the other hand, peripheral CD4 counts increased progressively over time. There was no correlation between HCV RNA (in log copies/mL) and CD4 counts.

In summary:

- 1: Hispanic ethnicity and lower AST levels were independently associated with HCV RNA-negativity in HIV patients with positive anti-HCV
- 2: HCV RNA levels in HIV coinfecting patients varies little over time, and
- 3: peripheral CD counts are not involved in the control of peripheral HCV viremia.

6. Abstract Number: 77

RENAL FUNCTION AND RIBAVIRIN DOSING IN CHRONIC HEPATITIS C

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A combination of interferon-alpha and ribavirin is standard therapy for chronic hepatitis C(HCV).Ribavirin

dosage is currently based on body-weight. The aim of this study was to critically evaluate current dosage recommendations on the basis of a population pharmacokinetic analysis. 398 ribavirin plasma concentration samples were collected from 63 patients undergoing treatment for HCV. 44 patients had normal range creatinine with an estimated glomerular filtration rate(GFR=estimated creatinine clearance) of 57-144 mL/min. Another 19 patients had renal impairment with a GFR of 5-57 mL/min. Population factors were age, gender, body-weight, serum creatinine and GFR. A population analysis was performed by non-linear mixed effect modeling. Ribavirin clearance was found to be linearly dependant on renal function with a small non-renal clearance dependant on body-weight. Renal function was a significantly better predictor of ribavirin clearance than body-weight alone. The volume of distribution was large and proportional to body-weight ($V=34,8 \times \text{body-weight}$), which resulted in a long half-life (100-600 hours depending on renal function) and a long time to steady-state (2-14 weeks). There was an inter-individual variability in ribavirin total clearance. In summary, ribavirin initial dosing should mainly be based on renal function and not as currently recommended, on body-weight alone. A ribavirin dosing schedule based on GFR and body-weight to reach an intended target concentration is proposed. Ribavirin monitoring is useful for optimizing HCV treatment not only in renal insufficiency, but also in other patients considering the time to steady state as well as the inter-individual variability in ribavirin clearance.

7. Abstract Number: 670

IMPACT OF METHADONE TREATMENT ON THE OUTCOME OF COMBINATION THERAPY FOR HEPATITIS C

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The rate of HCV-Infection among patients with a history of drug abuse is high. An increasing number of patients is treated with methadone maintenance therapy. Whether these patients are eligible for treatment of HCV remains controversial. The aim of this study was to evaluate the rate of side effects, patients stopping treatment, and SVR in HCV-infected patients on methadone maintenance therapy undergoing treatment with interferon-alpha/Ribavirin. We retrospectively analysed the data of 39 patients with former drug abuse and methadone therapy treated with 3-6MU interferon-alpha 2a/2b TIW and 1000-1200 mg Ribavirin daily over a period of 24(Genotype 2/3) or 48 weeks. To receive treatment all patients had to be at least 6 months stable on methadone treatment without any active substance abuse. Patients had to be in continuous treatment at the same methadone prescribing institution over at least this period. All patients had liver biopsy before treatment. Median age was 35.3(19-50), 26(67%) were male, 13(23%) female. 27(69%) had genotype 1, 10 (26%) genotype 3 and 2(5%) genotype 2. SVR was defined as HCV-RNA neg. at 24 weeks after treatment. Treatment had to be stopped in 2(5%) patients because of active drug abuse and in 2(5%) because of side effects. 18 patients (46.2%) had SVR (genotype 1 33%, genotype 2/3 75%). Treatment with Interferon-alpha/Ribavirin for patients with methadone therapy results in the same rate of SVR as in other patients. The rate of drug relapse and severe side effects is low. Long-term methadone therapy in stable patients is no contraindication for HCV-therapy.

8. Abstract Number: 655

TWO DOSES OF PEG-INTERFERON ALFA 2B PLUS RIVABIRIN IN GENOTYPE 1 NAÏVE PATIENTS WITH CHRONIC HEPATITIS

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PEG Interferon (PEG-IFN) plus ribavirin achieves a higher response rate than standard combination therapy in genotype 1. To evaluate the efficacy of two doses of PEG INF and ribavirin in 55 randomized patients. Twenty-eight received a high-weekly PEG-IFN alfa-2b dose (3 µg/kg for 1 week, 1.5 µg/kg for 3 weeks, and 1.0 µg/kg for 44 weeks) and 27, a low dose (0.5 g/kg) for 48 weeks. All received ribavirin 800 mg daily. HCV-RNA was analyzed by Real-time RT-PCR (100 copies/ml) at baseline, daily for 1 week, and at weeks 4, 8, 12, 24, 48 and 60. Initially, 3-µg/kg significantly inhibited HCV-RNA compared with 0.5-µg/kg (4.23 vs. 1.2 vs. 3.09 vs. 1.04 log; P <.001). Over therapy, a progressive, slower viral decrease occurred with both doses. HCV-RNA became undetectable faster and in more patients with the high dose: week 4; 22% vs. 7%, week 12; 56% vs. 44%, week 24; 69% vs. 63% and end-of therapy and follow-up; 71% vs. 61%. Seven percent of patients on the low dose vs. 14% on the high dose discontinued therapy. In conclusion, a high PEG-IFN dose plus ribavirin produces a more significant and faster decline in HCV-RNA levels than a low dose and a higher rate of sustained response. However, more patients needed to discontinue therapy.

9. Abstract Number: 404

HCV-HIV COINFECTION AND HIGHLY ACTIVE ANTIRETROVIRAL THERAPY: EPIDEMIOLOGICAL AND CLINICAL ISSUES

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The prevalence of HCV infection in HIV-infected persons ranges from 30% to 50%, depending on the population and increasing among i.v. drug addicts. Efficacy of HAART in coinfecting individuals maybe limited by a treatment-related liver toxicity. Retrospective chart review of HIV-infected patients referring to our tertiary care outpatient center during a 2-months period and treated with HAART since at least 6 months was performed. Of 270 study subjects (140 i.v. drug users, 49 homosexuals, and 81 heterosexuals), 36% and 5% were coinfecting with HCV and HBV, respectively; the prevalence of these infections was significantly higher among i.v. drug abusers (64% and 8%, respectively). Besides two nucleoside reverse transcriptase inhibitors (NRTI), ongoing HAART in 96 HCV-HIV coinfecting persons included one or two protease inhibitors (PI) in 51 patients, a nonnucleoside reverse transcriptase inhibitor (NNRTI) in 33, and a PI+NNRTI combination in 12. A transaminase elevation was observed in 28 patients (29%): 15 (29%) in PI group, 10 in NNRTI (30%), and 3 (25%) in PI+NNRTI. In 161 HIV-infected persons without HCV or HBV infection, increased transaminases were reported in only 21 patients (13%). In summary, the prevalence of HCV infection is considerably higher among HIV i.v. drug user patients, and hepatotoxicity associated with HAART may be worsened by the coinfection, while transaminase elevation seems irrespective of the selected antiretroviral regimen

10. Abstract Number: 5385

STEATOSIS EVOLUTION IS A MAIN DETERMINANT OF FIBROSIS PROGRESSION IN UNTREATED PATIENTS WITH CHRONIC HEPATITIS C

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The aim of this work was to study in untreated patients with chronic hepatitis C (CHC) and paired liver biopsies the spontaneous evolution of steatosis and its impact on fibrosis progression. Among 558 patients

with CHC who underwent a liver biopsy between 1996 and 1999, 96 (M/F 59/37; age 41±11 yo) were selected according to the following criteria: 2 liver biopsies available, absence of cirrhosis on the first biopsy, absence of antiviral treatment between the 2 biopsies, absence of co-infection with HBV or HIV. Steatosis was graded as none, mild-moderate (less than 30%), or severe (more than 30%). Histological lesions and steatosis evolution were examined by comparison of activity (A), fibrosis (F) and steatosis grades (METAVIR) between the 2 biopsies: improvement (lower or equal to -1), stability (0), worsening (upper or equal to 1). Fibrosis progression was observed in 31% of patients and stability in 69%, over a period of time of 48±32 months (10-176). Histological activity worsening was observed in 30% of patients, stability in 66%, and improvement in 4%. Steatosis was found in 54% of patients at first biopsy, and was severe in 10%. Steatosis worsening was observed in 36% of patients, stability in 50% and improvement in 14%. Among all factors tested in multivariate analysis, the only factor independently associated with fibrosis progression was steatosis worsening (worsening vs improvement/stability OR=4.7 [CI 95%:1.8-12.3], p=0.0001). In summary our results suggest that in untreated patients with CHC and paired liver biopsies, fibrosis progression is mainly related to worsening of steatosis.

11. Abstract Number: 5070

DETECTION OF HCV-RNA IN SALIVA OF PATIENTS WITH CHRONIC HEPATITIS C VIRUS INFECTION

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The aim of this study was to determine the prevalence of HCV-RNA in saliva from serum HCV-RNA positive patients by a highly sensitive PCR method. The study population included patients with chronic hepatitis C virus infection. HCV-RNA detection was performed in 61 saliva samples using a nested RT-PCR technique. The sensitivity of the technique was determined by studying the products of the PCR at serial plasma dilutions (100%, 10%, 1%, 0.01% and 0.001%) in saliva. The detection limit of this technique was 10 HCV-RNA copies/ml. A Hem-Check-1 kit based in monoclonal antibodies (Menarini Diagnostics, Barcelona) was used in order to search for the presence of hemoglobin (hidden blood). HVC-RNA was found in 32 out of 61 saliva specimens (52.4%). The presence of HCV-RNA sample was not related to the stimulated whole saliva production. No correlations were found between HCV detection in saliva and age, sex, identified risk factors for HCV infection, time lapsed since the diagnosis, AST, ALT, and GGT values. Hemoglobin was detected in 14 out of 61 saliva samples (22.9%), but its presence was not a predictor of HCV-RNA in saliva. A statistically significant relationship between serum HCV-RNA viral load and saliva HCV-RNA detection was observed (p<0.001). In summary this study suggests that HCV-RNA is present in saliva in a high proportion of HCV chronic infected patients and that the best predictive factor for HCV detection in saliva was a high level of serum HCV-RNA.

12. Abstract Number: 229

IS SUSTAINED VIROLOGIC RESPONSE DURABLE IN PATIENTS WITH CHRONIC HEPATITIS C TREATED WITH INTERFERON ALFA WITH OR WITHOUT RIBAVIRIN?

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Treatment of chronic hepatitis C using interferon alfa alone (IFN) or with ribavirin (IFN/RBV) is capable of inducing a sustained virologic response (SVR). The aim of this study was to assess the durability of SVR in these patients. Between 1994 and 2000, 256 patients with chronic hepatitis C were treated with IFN (n=61)

or IFN/RBV (n=195) for 24 to 48 weeks. At the end of the 6 month post treatment follow up 60 patients were SVR: 6/61 (10%) with IFN; 54/195 (28%) with IFN/RBV. All patients signed informed consent and were evaluated annually using in house qualitative PCR (limit of detection: 200 copies/ml). Among the 60 patients with SVR, 41 (68%) were males. Mean age was 42 +/-12 years (18 to 64). Mean follow-up was 20 +/- 13 months (1 to 58). HCV genotype was available in 45 patients (12 type 1; 33 type 2 or 3). There was cirrhosis in 12/59 (20%) and transition in 8/59 (14%) patients biopsied pre-treatment. Follow up time was the following: A) less than 12 months (n=17); B) 12 to 23 months (n=20); C) 24 to 35 months (n=15); D) 36 to 48 months (n=5), and E) more than 48 months (n=3). Only 2 patients relapsed, albeit transiently, with a positive then negative HCV-RNA (both within 2 years and both in the IFN/RBV group). No patients decompensated during follow-up and 97% maintained normal ALT levels. In summary, patients with chronic hepatitis C who achieved a SVR remained HCV-RNA negative during follow-up.

13. Abstract Number: 416

THE EARLY DECREASE OF HEPATITIS C VIRUS CORE ANTIGEN IN THE SERUM OF CHRONIC HEPATITIS C PATIENTS PREDICTS DRUG EFFICACY AND PRIMARY RESPONSE TO ANTIVIRAL THERAPY

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Quantification of hepatitis-C-virus-core-antigen (HCVcAg) in serum might be useful to monitor HCV dynamics during therapy. We measured HCVcAg and HCV-RNA in 275 sera of 28 patients (baseline, 48 hours, 7, 14, 28 days and monthly during treatment) and HCVcAg diagnostic accuracy (DA) to identify (within one month of treatment) 16 primary responders (PR, normal aminotransferase and undetectable HCV-RNA after 3-6 months). Interferon-alfa (3-6 MUI tiw) without/with Ribavirin (10.6 mg/kg/day) were given for 6-12 months. We used Cobas-Amplicor-HCV-Monitor 2.0 Roche-Molecular-Systems (quantitative cut-off 600 and qualitative 50UI/l) and HCVcAg ortho-Clinical-Diagnostics (cut-off 1.5pg/ml). HCVcAg and HCV-RNA levels correlated significantly (Pearson's-correlation-coefficient, $r=0.799$, $p<0.001$) as well as their dynamics. Using HCV-RNA qualitative assay as gold-standard HCVcAg showed 61.7% sensitivity, 97.4% specificity and 66.6% DA. A cut-off (0.86pg/ml) identified by ROC-analysis increased the assay sensitivity (73.8%) with 94.9% specificity and 76.7% DA. We observed the block of virion release (HCV-RNA decrease ≥ 0.7 log at 48 hours) in 22 patients (15 of 16 PR, 94%): the HCVcAg Delta Variation (DV) of 84.3% showed 77.3% sensitivity, 100% specificity in its identification. After one week, 96.6% HCVcAg DV showed 90% positive predictive value (PPV) and 71.4% DA to identify PR: the HCV-RNA-DV of 92.4% showed 75% PPV and 50% DA. After one month quantification of HCVcAg (DV, 98.75%) and HCV-RNA (DV, 99.42%) showed the same PPV (92.9%) and DA (88.8%). HCV serum levels correlate with those of HCV-RNA. An early HCVcAg variation ≥ 1 log predicts drug efficacy and primary response.

14. Abstract Number: 5149

HIGH PREVALENCE OF HELICOBACTER PYLORI IN AN ISRAELI ETHNICALLY HETEROGENEOUS HEPATITIS C POPULATION: INNOCENT BYSTANDER OR MORE?

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Antibodies to Helicobacter pylori (Hp) have been found in 89% of 254 Italian HCV patients, all cirrhotic (1). It has also been suggested that differences in the progression of chronic Hepatitis C (HCV) may be due to a

cofactor stemming from coinfection by bacteria (Hp) (2). Object: To determine: 1) the prevalence of Hp in Israeli HCV patients; 2) are there similar factors; 3) if the natural history of HCV differs in Hp-infected patients. 72 serologic positive HCV patients were tested for HCV-RNA (by nucleic acid amplification), and genotype (by sequencing), Hp IgG (ELISA) and 2 of the following: urease test, Giemsa staining, 13C-UBT. Liver disease was assessed by clinical, biochemical, and histological data while sociodemographic survey was conducted. The cohort included 35 males and 37 females (mean age: 52.9 years; range 18-80). Six patients were born in Israel; 66 immigrated from Eastern Europe (52), North Africa (6), and Asia (8). HCV-RNA was found in 58/72 (80.5%) and Hp in 62/72 (86.2%). Eight, all Hp infected, had cirrhosis, of which 3 decompensated. In summary in these 72 HCV patients, prevalence of Hp is very high (86.2%); low socioeconomic level is a common factor; the 2 diseases apparently do not interact, however, eradication of Hp is strongly advised. 1) J Hepatol 33:648-50, 2000; 2) Med Hypothesis 54:275-7, 2000.

15. Abstract Number: 242

CHRONIC HEPATITIS C (CHC) DOES NOT IMPAIR THE PHYSIOLOGIC INCREASE OF ERYTHROPOIETIN (EPO) PRODUCTION IN RESPONSE TO THE RIBAVIRIN (RBV)-INDUCED ANEMIA

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Interferon and RBV combination is the treatment of choice for CHC. RBV administration is associated with the development of hemolytic anemia, which appears early during treatment and progresses to a nadir value during the first 4-8 weeks of therapy. We observed that EPO concentration in serum of HCV positive subjects increases significantly in response to anemia caused by RBV. The aim of this study was to further investigate whether EPO response to the RBV-induced anemia was impaired in CHC by comparing the results obtained in 18 patients (median age, 59 years [24-73]; M/F, 11/7) before and during RBV treatment with those obtained in 10 anemic, otherwise healthy control subjects (Flaharty KK. Pharmacotherapy 1990; 10:9S-14S). Serum EPO was measured at baseline and at the hemoglobin concentration nadir with the DiaSorin EPO-Trac I125 radioimmunoassay. By plotting individual values describing the relationship between hemoglobin and EPO concentrations in serum of CHC patients - before treatment and at the hemoglobin nadir during RBV administration - together with those obtained in control subjects, we found that the range of EPO response pattern for the degree of anemia was overlapping in the two patient groups. In CHC patients serum EPO levels associated with RBV-induced anemia tend to fall into the range of EPO responses seen in non hepatic anemic subjects. This suggests that the chronic liver damage by HCV affects anemia-induced EPO response to RBV induced-anemia to a minor extent. The role that EPO synthesis plays in the above clinical setting deserves further evaluation.

16. Abstract Number: 5177

IMPACT OF SMOKER'S POLYCYTHEMIA ON CLINICAL AND LABORATORY FEATURES AND ON THE RESPONSE RATE TO INTERFERON-ALPHA IN CHRONIC HEPATITIS C (CHC) PATIENTS

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Objective: To highlight the clinico-pathological aspects of smokers polycythemia in CHC patients and to

compare the sustained virological response (SVR) to interferon- α therapy in heavy smokers to non-smokers. Over the year 1998, 122 CHC male patients presenting to Cairo Liver Center, were divided according to smoking habits into heavy smokers (>2 packs/day) 38 patient and non-smoker group 84 patients respectively. Both groups were studied as regards clinical presentation, level of transaminases, haemoglobin and, haematocrit values as well as serum iron and uric acid. Liver biopsy and iron staining was performed in 23 patients in group 1 and 68 in group 2. IFN- α 3MU TIW was given for 6 months to 32 patients in group 1 and 62 in group 2 with SVR evaluated. All heavy smokers presented with facial flushing, warm palms, fullness in the head, dizziness, lethargy, generalized parathesia, pruritus, arthralgia. All smokers had haemoglobin level >16 g/dl and haematocrit >55 compared to 12/84 (14.3%) in group 2. Serum iron was raised in 12/38 (31.6%) in group 1 compared to 8/84 (9.5%) in group 2. Hyperuricemia was reported in 18/38 (47.4%) in group 1 compared to 6/84 (7%) in group 2. Repeated phlebotomy corrected both symptoms and laboratory derangement. SVR was higher 7/62 (11.3%) in non-smokers compared to smokers 2/32 (6.3%) but didn't reach statistical significance ($p=0.06$). In summary heavy cigarette smoking induces polycythemia with multiple adverse clinical and laboratory manifestations correctable by therapeutic phlebotomy. Smokers tend to have lower SVR and should refrain from smoking before starting IFN- α therapy.

17. Abstract Number: 619

DECREASED BONE MINERAL DENSITY IN NONCIRRHOTIC PATIENTS WITH CHRONIC HEPATITIS B OR C

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Several previous studies suggest that loss of bone mineral density is common among patients with chronic liver diseases. We studied bone mineral metabolism and density in patients with chronic hepatitis B or C without cirrhosis. Biochemical markers of bone turnover and bone mineral density were measured in 42 consecutive patients. They are suffering from viral hepatitis B (n=13) and hepatitis C (n=29). Bone mineral density was measured by dual x-ray absorptiometry in the lumbar spine and femoral neck. The values were expressed as the T and Z score. Bone metabolism markers and hormone profiles were measured. Bone mineral density were lower in 29 (69%) of our investigated 42 patients with chronic hepatitis B or C (femoral neck: $0.711 \pm 0.129 \text{ g/cm}^2$; lumbar spine: $0.951 \pm 0.126 \text{ g/cm}^2$). 8 of the 29 osteopenic patients (28%) have osteoporosis. T-score value in chronic Hepatitis C patients was more decreased (femoral neck T: -1.59 ± 0.98 ; lumbar spine T: -1.10 ± 1.09) compared with patients with chronic hepatitis B (femoral neck T: -1.31 ± 1.00 ; lumbar spine T: -0.79 ± 1.29). Serum and urine biochemical markers were within the normal limits in both groups. In summary, chronic hepatitis B or C in non cirrhotic patients may induce bone loss. In view of our results and according to previous studies this secondary effect of chronic hepatitis should be further investigated in following studies with larger number of included patients. Markers of bone metabolism and bone mineral density might be used in monitoring these patients to reduced their risk of developing osteoporosis.

18. Abstract Number: 5301

VIRAL KINETICS OF COMBINATION PEGYLATED INTERFERON α -2A AND RIBAVIRIN IN PATIENTS WITH HEPATITIS C CIRRHOSIS

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Recent advances in the management of hepatitis C include pegylated interferon and viral kinetics. Phase III studies of pegylated interferon demonstrate improved efficacy in previously difficult-to-treat groups, including cirrhotics. Rapid decline in viral levels may allow early identification of nonresponders. This study evaluates the use of viral kinetics in patients with HCV-cirrhosis receiving combination pegylated interferon alpha 2a (Pegasys) and ribavirin. 31 treatment-naïve HCV-cirrhosis patients received pegylated interferon-a 2a (PegasysTM) 180 mg/week and ribavirin 400mg bd for 48 weeks. Serum HCV RNA levels were measured at baseline, 2, 7 and 28 days, 3, 6, 12 and 18 months using the MonitorTM assay (Roche, Basel). HCV isolates were genotyped by INNOLiP^{ATM} line probe assay (Innogenetics, Antwerp). Rapid virologic response (RVR) was defined as at least 2 log drop in [HCV RNA] level at 28 days. Thrombocytopenia or neutropenia necessitated pegylated interferon dose reduction in 25/31 cirrhotic patients. RVR was achieved in 17/31 (55%) by 28 days. RVR occurred in 11/14 (79%) patients infected with Genotypes 2/3 compared to 6/17 (35%) infected with Genotype 1 (p=0.03). After 6 months, 15/19 (78%) were PCR negative, including 10/10 (100%) who achieved RVR and 5/9 (56%) who did not (p=0.033). Sustained virologic responses are awaited. Although adverse effects with pegylated interferon are common in cirrhotic patients, the rate of RVR is similar to noncirrhotic patients. If this study confirms similar predictive values of RVR to noncirrhotics, then failure of RVR should allow early treatment withdrawal in cirrhotics, thereby minimizing adverse effects and costs without jeopardizing chance of cure.

19. Abstract Number: 5390

HEPATITIS C AND DIABETES MELLITUS: WHAT IS THE CONNECTION?

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The objective on this study is to carry out a prospective study of baseline insulinemia in non-diabetic cirrhotic patients infected with HCV, comparing their values with those of a group of non-HCV non-diabetic cirrhotic patients. To research the factors involved in both groups in the increase of peripheral resistance to insulin. A trial including 32 HCV cirrhotic diabetic patients (Group I) and 41 non-diabetic cirrhotic patients of other aetiologies (Group II) was carried out. Baseline insulinemia as well as insulin resistance factors like age, anthropometric indices, stage of cirrhosis and iron plasma levels were compared. The average baseline insulinemia values in group I was 21.5 mU/ml (18.6-24.4), vs 14 mU/ml (10-18) in group II (p<0.001), and the percentage of hyperinsulinemia was 87.5% (72.5-95.9) vs 56% (40.8-70.6), respectively (p<0.01). No differences were observed in either group when comparing age, weight, height, body mass index and Child-Pugh staging score. Whereas serum ferritin levels in Group I patients were higher than those in Group II [123.3 (12.4-289.3) vs 65.5 (2.4-306) ng/ml, p<0.05]. Multivariate logistic regression study demonstrated that insulinemia values (OR=1.21; CI 95% 1.09-1.34, p<0.001) and ferritin levels (OR=1.21; CI 95% 1.02-1.052.69, p<0.04) were independent factors associated to HCV. In summary, HCV-positive non-diabetic cirrhotic patients have higher baseline insulinemia levels, as well as a greater prevalence of hyperinsulinemia than cirrhotics due to other aetiologies. This could be explained by an increase of peripheral insulin resistance, mediated by the increase of iron deposits in these patients, and may be responsible for the increased risk of developing diabetes mellitus.

20. Abstract Number: 343

HCV INFECTION SCREENING AND TREATMENT IN DRUG USERS FOLLOWED IN AN ADDICTION OUT PATIENT UNIT

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The aim of this study is to investigate efficiency of HCV screening and treatment of drug abusers (mostly heroin IV) enrolled in an addiction out patient program.

All patients followed in an addiction unit were offered HCV ab testing; further evaluation and treatment if indicated, were proposed to positive patients. Between July 1997 and September 2000, 404 consecutive patients (310 men; mean age: 32; 94 per cent in substitution program) were included. 66 per cent of patients agreed for HCV ab testing: 83,6 per cent had positive test. Among them, 68 per cent accepted to perform ALT serum measurement and HCV mRNA. 120 had indication for liver biopsy, 32 patients declined. 88 liver biopsies were performed, showing severe fibrosis (Metavir score F3 or F4) in 20 cases. Ethanol intake (over 50g per day in 51 per cent of patients) was significantly correlated to fibrosis. Antiviral treatment was indicated (Metavir score F2, F3 or F4) in 47 patients but was initiated only in 27 due to patient refusal (7) or contraindication (13). Treatment had to be discontinued in 12 cases because of psychiatric side effects (depression: 3 ; delirium: 3 ; severe irritability: 3 ; relapse in heroin addiction: 3). Finally, 12 patients completed the treatment by either interferon (4) or interferon and ribavirin (8). Only 4 were sustained responders. In summary, despite the high rate of indication for antiviral therapy, treatment benefit was low due to high drop out rate. Ethanol withdrawal must be the highest priority in these patients.

21. Abstract Number: 221

INTERFERON ALPHA-2b ALONE OR COMBINED WITH RECOMBINANT GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR AS TREATMENT OF CHRONIC HEPATITIS C

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The aim of this study is to compare the effect of interferon-alpha (INF-alpha) + granulocyte-macrophage colony-stimulating factor (GM-CSF) to INF-alpha alone in the treatment of chronic hepatitis C. 45 patients with chronic hepatitis C were randomized to 1) INF-alpha + GM-CSF for three months followed by INF-alpha alone for nine months (n=23) or 2) INF-alpha for 12 months (n=22). Both drugs were administered three times weekly in doses of 3 mU (INF-alpha) and 50-100 micrograms depending on body weight (GM-CSF). After 12 months, more patients treated with GM-CSF + INF-alpha compared to INF-alpha alone had normalized ALT (65 vs 32%, p=0.03), but there was no difference in viral clearance (48 vs 32%, p=0.27). After 6 months follow-up, the biochemical response had declined to 35% in the combination therapy group and to 23% in the monotherapy group (p=0.37), viral clearance had declined to 22 vs 27% (p=0.67) and the overall sustained response rate was 22 and 23% respectively (p=1.00). One patient, from the monotherapy group, had the dose of INF-alpha transiently reduced due to neutropenia. In summary, although INF-alpha + GM-CSF had significantly better effect on the biochemical response during treatment compared to INF-alpha alone, the sustained biochemical and virological response was not increased. Thus, GM-CSF hardly plays any role in the future treatment of chronic hepatitis C, except for treatment of INF-alpha induced neutropenia.

22. Abstract Number: 622

QOL BENEFITS OBSERVED AS EARLY AS WEEK 2 WITH PEGINTERFERON ALFA-2A (40KD) (PEGASYS) IN COMBINATION WITH RIBAVIRIN (RBV) VERSUS INTERFERON ALFA-2B PLUS RBV

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The objective on this study is to determine the relationship of time-on-therapy to QoL during treatment with peginterferon alfa-2a (40KD) + RBV versus IFN + RBV. Patients were treated for 48 weeks with peginterferon alfa-2a (40KD) + RBV or IFN + RBV and followed for an additional 12 weeks. QoL was assessed using the SF-36 and Fatigue Severity Scale (FSS). Scores were analyzed with a repeated-measures mixed-model ANCOVA. For both treatment groups, QoL scores declined from baseline to week 2, declined further by week 12, and then remained stable through week 48. QoL was better for the peginterferon alfa-2a (40KD) + RBV group at week 2 on all scores, at week 12 on 6 SF-36 domains and FSS, and at weeks 24 and 48 on all scores. Differences were statistically significant at week 2 for Role-Physical and FSS, and at weeks 2 and 24 for Bodily Pain, Vitality, and Social Functioning. Consistent with improved QoL, patients in the peginterferon alfa-2a (40KD) + RBV group reported fewer complaints of pain and fatigue interfering with activities including work compared with the IFN + RBV group. In summary, advantages in QoL favoring peginterferon alfa-2a (40KD) (Pegasys) + RBV emerge as early as week 2 and continue throughout therapy. These results are consistent with lower rates of flu-like symptoms and depression for peginterferon alfa-2a (40KD) + RBV. More favorable QoL should reduce premature discontinuation.

23. Abstract Number: 213

INEQUALITIES IN ACCESS TO HEALTHCARE OF HEPATITIS C PATIENTS IN A GENERAL POPULATION

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Our aim was to study the management of patients after hepatitis C diagnosis in the 1,006,171 inhabitants of the French population. A questionnaire was sent to practitioners who had pointed out hepatitis C cases to obtain complementary information. Between 1994 and 1999, 1508 HCV cases were diagnosed, of which 1251 were eligible for the study. A total of 201 (16.1 %) patients did not have specialized medical care after diagnosis; among them 55.2 % had normal ALT, 58.2 % had risk factors related to lifestyle (drug addiction, sexual risk) and 22.4 % were current alcoholics. Amongst the 1050 other patients, 441 (42.0 %) had a liver biopsy and 263 (25.1 %) were treated. Multivariate analysis showed that treatment was more often carried out in males than in females ($p = 0.003$), in patients under 65 than in older patients ($p = 0.0002$), in patients diagnosed by general practitioners or by gastroenterologists than by another specialist ($p = 0.0002$), in non alcoholics patient or in former alcoholics than in current alcoholic patients ($p < 5 \cdot 10^{-5}$). Main non treatment reasons were normal ALT (42.4 %) and contraindication to treatment (18.3 %); differences according to the gender were found, particularly alcohol consumption and drug addiction more frequent in males than in females ($p = 0.001$ and $p = 0.04$). This study showed that in a general population one patient out of six remained out of healthcare progression. It revealed differences in management according to gender which

need further investigations.

24. Abstract Number: 5514

CONCORDANCE BETWEEN ANTI HCV AND HCV RNA AMONG PATIENTS WITH AND WITHOUT BIOCHEMICAL EVIDENCE OF LIVER DISEASE

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All consensus recommendation for therapy in HCV suggests HCV RNA positivity as an important prerequisite. Concordance between anti HCV positivity and HCV RNA among patients with elevated ALT has been reported to be quite high. Therefore we evaluated the frequency of HCV RNA positivity among patients with elevated ALT and anti HCV positive and compared with similar frequency among anti HCV positive healthy blood donors without elevated ALT. A total of 1785 healthy blood donors without any overt clinical disease with normal ALT and 116 patients with elevated ALT (more than 1.5 times) and anti HCV positivity were included. We also included patients with elevated ALT without anti HCV positivity. All these three groups of patients were screened for HBV, HAV, HEV infection. There were 65 blood donors, 116 patients with raised ALT and anti HCV positivity, and 30 patients with raised ALT but without any serological markers of hepatitis viral infection including anti HCV. HCV RNA was detected in 8/65 of blood donors, 110/116 among patients having anti HCV positive and raised ALT and 29/30 among patients having only raised ALT. In summary, 97 percent patients with raised ALT without B, A and E had HCV RNA positivity and 97 percent patients with raised ALT and anti HCV positive had HCV RNA positive where as only 12percent of patients had HCV RNA positive despite having anti HCV positive with normal ALT.

25. Abstract Number: 476

FACTORS ASSOCIATED WITH STEATOSIS AND RELATIONSHIP BETWEEN STEATOSIS AND THE SEVERITY OF THE DISEASE IN PATIENTS WITH CHRONIC HEPATITIS C

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To identify the factors associated with steatosis in patients with chronic hepatitis C, 134 patients (85 men, 49 women, mean age 43.9 * 11.8 years) with chronic hepatitis C were studied. Steatosis was graded as absent, mild (< 10% of hepatocytes), moderate (10 to 30%) or marked (> 30%). Activity and fibrosis were determined according to METAVIR and Knodell. BMI, route of transmission, duration of the disease, presence of diabetes and arterial hypertension, tobacco and alcohol consumption, level of ALT, GGT, glucose, cholesterol, triglycerides and ferritin, liver iron overload, HCV genotype and viral load were determined in all the patients. Moderate or marked steatosis was found in 28% of the patients. In univariate analysis, alcohol consumption > 20 g/day (52% of moderate or marked steatosis, p=0.003), BMI > 25 kg/m² (40%, p=0.02), increased GGT level (69%, p<0.001), genotype 3 (52%, p=0.005), moderate or severe activity (84%, p<0.001), severe periportal necrosis (81%, p<0.001) and marked fibrosis or cirrhosis (43%, p<0.001) were associated to moderate or marked steatosis. In multivariate analysis, moderate or marked steatosis was independently related to alcohol consumption > 20 g/day (OR=5.8; 95% CI (1.5-21.9)), BMI > 25 kg/m² (OR=3.9; 95% CI (1.3-11.6)), genotype 3 (OR=4.0; 95% CI (1.2-13.3)) and moderate or severe activity (OR=5.1; 95% CI (1.5-17.9)). In summary, these results show that in patients with chronic hepatitis C, moderate or marked steatosis is not only associated to BMI > 25 kg/m², alcohol consumption and genotype 3, but also to the severity of activity.

26. Abstract Number: 5241

PREDICTIVE VALUE OF TWENTY-FOUR-HOUR QUANTIFICATION IN INTERFERON THERAPY OF CHRONIC HEPATITIS C USING DIFFERENT TYPES OF INTERFERON

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In a prospective study we used 3 different interferon-types to determine whether the viral-decline in the first 24 hours of interferon-application is of predictive value for the ETR. 31 untreated patients (23 male, 8 female) with chronic hepatitis-C. After liver-biopsy group A (15) received standard-IFN-alpha-2a (Roferon), Group B (16) either 12-kD-PEG-IFN-alpha2b (PEG Intron) or 40-kD-PEG-IFN-alpha2a (Pegasys). After a single-dose of interferon the viral-decline was measured exactly 24 hours later. Interferon/ribavirin combination was continued for 12 months in genotype 1 (18), 6 months in genotype non1 (12) with the same type of interferon as in the initial dose: 6MU IFNalpha2a-TIW, 80/100mcg 12kD-PEG-IFN-alpha2b/per week adopted to the body weight, 180mcg-40kD PEG-IFN-alpha-2a/week. Ribavirin doses were 1000mg < 70kg body-weight, 1200mg > 70kg body-weight. Therapy was stopped in non-responders after 6 months combination therapy. Quantifications were done at start and exactly 24 hours after the initial-dose, then every 3 months with the Cobas-Amplicor-HCV-MonitorTM-Test (v2.0, Roche-Diagnostic). Qualitative-PCR was done with Cobas-AmplicorTM-HCV-Test (v2.0) every 3 months during therapy and during follow up. ETR and SR were defined by PCR-method. Pretreatment viremia ranging from 210,000 to 1,600,000 IU/ml (mean 657,129). Statistic analysis was done to find out the probability of responding or non responding. Overall ETR was 48%, 36% in genotype-1, 66.6% in genotype non-1. ETR in group A was 46.6%, in group B 50%. 40% of group A showed a 24-hour viral decline of more than 80%, 68.7% in group B. Patients having a viral reduction of less than 80 percent after the initial dose had a probability of non-responding in 93% (88.8% in group A, 100% in the group B). Viral reduction of more than 80% had a probability of non-responding in 11.7% (0% in group A, 18.2% in group B). In summary there is a high significance to predict the probability in non-response in patients having less than 80% viral-reduction during the first 24 hours. Twenty four hour quantification seems to be of the same predictive value in different genotypes and interferons.

27. Abstract Number: 1

PREDICTIVE MARKERS OF THERAPY OUTCOME IN CHRONIC HEPATITIS C

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The aim of this study was meant to identify predictive markers of failure or of success in the treatment of patients with chronic hepatitis C. Depending on the predictive markers, the physician can modulate the therapeutic regimen. Using the Stouffer method and Meta 5.0 software, a meta-analysis was carried out of the studies related to this topic, published between 1997-2000. The level of statistical significance for each predictive marker is indicated and also the number of studies with opposite outcome which must be introduced in the meta-analysis in order to make the p value associated to the analysed predictive marker statistically insignificant (>0.05) – Fsf parameter. As predictive markers of good outcome of IFN + ribavirin therapeutic regimen, the following factors were identified: low levels of GGT ($p < 0.0001$, Fsf = 35), initial serum HCV RNA < 2 mil. copies/ml ($p < 0.0001$, Fsf = 38), genotype non-1b ($p = 0.0027$, Fsf = 9), minimal or no fibrosis ($p = 0.036$, Fsf = 1). In case of retreatment after a previous course of IFN (in monotherapy), the relapsers have a better chance of sustained response ($p < 0.001$, Fsf = 16). As predictive markers of therapy failure, which can be identified before the treatment starts, the following factors were identified: initial serum HCV RNA > 2 mil. copies/ml ($p = 0.0017$), low levels of ALT ($p < 0.03$), a reduced amount of IFN alpha receptor mRNA ($p = 0.00275$), high pretreatment levels of serum IL10 ($p < 0.01$). Predictive markers

of the negative outcome of the therapy which can be identified after the beginning of the treatment are: HCV RNA detectable after the first month of therapy, abnormal ALT values after 12 weeks of treatment, loss of initial quasispecies and frequent emergence of new variants ($p < 0.0001$), detection of anti-IFN antibodies during treatment ($p < 0.0005$), high and persistently altered plasma alpha GST levels ($p < 0.005$). In summary, a positive HCV RNA test at week 4 is a better therapy stopping criterion than abnormal ALT at week 12. The therapy outcome can be accurately monitored by the level of serum alpha GST. It is necessary to individualize treatment and to give, from the beginning, a combined or a more aggressive therapy to patients with chronic hepatitis C, decreasing the risk of cirrhosis and hepatocellular carcinoma, which persist without viral eradication.

28. Abstract Number: 4

WHAT CAN BE DONE FOR PATIENTS WITH CHRONIC HEPATITIS C, WHICH HAVE FAILED TO RESPOND TO INTERFERON MONOTHERAPY?

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Chronic hepatitis C is a major public health problem with a prevalence around 3%. Although interferon alpha (IFNa) monotherapy isn't the standard therapeutic regimen anymore, a large number of patients have been treated just with IFN in the past and only 15-20% of them have had a sustained response. It is important to evaluate the alternative treatment regimens available for IFN monotherapy non-responders (NRs) or relapsers (Rs), because eliminating the viral infection is an important goal. A meta-analysis was carried out of the studies related to this topic, published between 1997-2000. A total of 1857 patients with chronic hepatitis C (NRs or Rs after IFN monotherapy) who had participated to the trials included in the respective studies, were treated with: elevated doses of IFN, IFN+ribavirin, IFN+amantadine+ribavirin or Consensus interferon (CIFN). Follow-up after therapy was 6 or 12 month and sustained response (SR) was established depending on ALT normalization and HCV RNA negativity. The meta-analysis indicates the following probability of SR for relapsers after IFN monotherapy: 16.5% after IFN in higher dose retreatment, 44.3% after IFN + ribavirin and 42.5% after CIFN. Regarding non-responders, the SR after retreatment is: IFN in higher dose - 3.1%, IFN + ribavirin combination therapy - 12.7%, IFN + amantadine + ribavirin - 40%, CIFN - 13%. In summary, higher dose of IFNa for the retreatment of IFN previous non-responders has a very low rate of SR and should be avoided. IFN + ribavirin or CIFN are viable alternative treatment regimens for the IFN monotherapy failure. Triple therapy with IFN, amantadine and ribavirin seems to be the treatment of choice for IFN monotherapy non-responders, but it needs further investigation. An individualized and aggressive therapy should be considered from the beginning. It should be modulated afterwards depending on the predictive markers of the treatment outcome.

29. Abstract Number: 273

CLINICAL SIGNIFICANCE OF MIXED CRYOGLOBULINEMIA IN CHRONIC HEPATITIS C PATIENTS

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The aim of this study is to assess the relationship between the presence of mixed cryoglobulinemia /CG/ and some characteristics of the chronic hepatitis C /CH-C/. 207 patients (107 M and 100 F, mean age 38,2) with CH-C were studied. 88(42,5%) of them were cryoglobulinemic /CG+/. We compared the clinical, histological (in 178 patients) characteristics and response to interferon-alpha/IFN/ monotherapy (in 66 patients, 3ME, tiw) in CG+ and CG- groups of patients. Necroinflammatory activity and fibrosis were scored according to METAVIR. CG+ was associated with female sex ($p < 0,001$), older age ($p < 0,0001$), longer

disease duration ($p < 0,0001$) and liver cirrhosis ($p < 0,0001$). Stage of fibrosis was significantly higher in CG+ patients ($p = 0,0001$) whereas the activity grades and mean ALT levels were statistically similar in two groups. CG+ was associated with titer of rheumatoid factor, prevalence of extrahepatic manifestations (CG-related vasculitis, some hematological and autoimmune syndromes). The sustained virological response rate to IFN was lower in CG+ patients ($P < 0,05$) and clinical improvement of CG-related symptoms was transient. But according to the results of logistic regression analysis CG+ was not an independent negative predictive factor (age, disease stage were predictive). In summary, patients with CG+ had increased fibrosis and incidence of cirrhosis. CG+ may be a cause or an effect of increased hepatic fibrosis. Fibrosis can influence the response rate to IFN treatment in this patients. Prognostic significance of CG in course of CH-C needs further evaluations.

30. Abstract Number: 361

CHANGES IN LIPID METABOLISM IN CHRONIC HEPATITIS C

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Liver steatosis is common in patients with chronic hepatitis C (CH-C), occurring in approximately 50% of biopsy specimens. Data suggests interactions between HCV and lipid metabolism. The aim of this study was to assess relationship between degree of steatosis and serum lipid levels in CH-C patients. 114 CH-C patients were studied compared to patients with steatosis of other reasons and negative for HCV. Paraffin-embedded biopsy materials were analysed using Knodell scoring system. Steatosis was graded semiquantitatively as: absent (grade 0); mild (involving less than 10% of hepatocytes, grade 1); moderate (involving 10-30%, grade 2); severe (involving more than 30%, grade 3). Alanine aminotransferase (ALT) activity, total cholesterol and triglyceride concentrations, presence of HCV RNA were measured in sera of patients. Statistical analysis was performed by ANOVA on Ranks. Steatosis was detected in 84 CH-C specimens (74%). ALT levels were significantly higher in patients with grade 3 steatosis in the CH-C group, compared to grade 0 steatosis with CH-C ($p < 0,05$). Total cholesterol and triglyceride concentrations in patients with steatosis only (without HCV) were significantly higher ($p < 0,05$) than in patients with CH-C with or without steatosis. HCV infection is significantly associated with steatosis in CH patients, resulting decrease of cholesterol and triglyceride compared to patients with steatosis only.

31. Abstract Number: 499

PRIMARY IFN-RESISTANCE IN CHRONIC HEPATITIS C VIRUS GENOTYPE 4 INFECTION

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The objective of this study is to study primary IFN-resistance (as defined by the response to a test dose of IFN, Jessner et al, Lancet 2001) in HCV genotype 4 infection as predictor for outcome of IFN/ribavirin therapy. Treatment-naive pts with chronic hepatitis C due to genotype 4 received a single dose of 10MU IFNalpha2b (IntronA) one week before treatment with 5MU IFN/d for 2 weeks (days -14 to -1). Thereafter combination therapy with 5MU IFNalpha2b/2d or 1.5microg/kg PEG-IFNalpha2b (or PEGIntron, Aesca-SPI) plus 1000-1200mg ribavirin/d was initiated. Viral load was determined using the Cobas Amplicor Monitor HCV Assay v2.0 before and 24h after 10MU, before and after the first 5MU dose (days -14 and -13), and on days -7 and -1. Viral load decreased by median 1.40 logs (range 0.27-1.91) and 0.95 (0.13-1.77; $p = 0.028$), 24h

after 10 and 5 MU IFN, respectively. Currently, 10 pts have completed 3-months combination therapy and 6 became virologic responders within 3 months. In responders, the log change in viral load 24 hrs. after 5 MU IFN was 1.28 (0.90-1.77) and in nonresponders 0.40 (0.13-0.46; $p=0.011$). After 14 days on daily 5MU IFN it was 2.97 (2.20-3.41) in responders and 0.40 (0.27-0.74; $p=0.011$) in nonresponders, respectively. In summary, for HCV genotype 4 the initial response to IFN is similar to HCV genotype 1, it is dose-dependent and some strains are primary IFN-resistant. A decrease in viral load of more than 0.5 log 24h after 5 MU IFN is an excellent predictor of on-treatment virologic response.

32. Abstract Number: 492

HIGH DOSE INDUCTION THERAPY WITH CONSENSUS INTERFERON AND RIBAVIRIN FOR TREATMENT-NAIVE PATIENTS WITH HEPATITIS C

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Treatment with interferon alfa and ribavirin has an efficacy in chronic hepatitis C patients with sustained response rates of about 40%. However, response in genotype 1 patients with high viral load is considerably lower. Recent studies have shown improved response rates using consensus interferon (CIFN) in genotype 1 and high viral load patients. In the present study, the efficacy of CIFN induction therapy followed by combination with ribavirin in naive patients with chronic hepatitis C is evaluated. A total of 300 patients have been included. All patients had histologically proven hepatitis, elevated ALT values and were viremic; 73 % had genotype 1. Patients are treated with CIFN with 27 or 18 ug QD for 4 weeks, followed by 18 or 9 ug QD for 8 weeks. Treatment is continued with CIFN at 9 ug QD with and without ribavirin (7.5 or 15 mg/kg/d) for another 36 weeks. At 12 weeks therapy an undetectable HCV-RNA was observed in 87 and 72% in the CIFN 27/18 and 18/9 ug groups, respectively. Due to side effects CIFN had to be reduced in 13% and discontinued in 7% of patients. 98% of genotype 2/3 patients and 67% of genotype 1 patients have so far responded. CIFN daily dosing/ induction therapy thus shows significant response rates comparable to PEG-IFN / ribavirin combination especially in genotype 1, high viral load patients. The further follow-up will show the additional effect of ribavirin and whether the initial high response rates will translate into corresponding sustained response rates.

33. Abstract Number: 663

EVALUATION OF LIVER FIBROSIS BY COMBINED SERUM MARKERS IN CHRONIC HEPATITIS C PATIENTS TREATED BY INTERFERON ALPHA AND RIBAVIRIN

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Our aims were to evaluate the diagnostic ability of a panel of serum markers to stage liver fibrosis and to determine their kinetic during antiviral therapy. Among 194 naive patients with liver biopsy, 76 were treated by IFN and ribavirin for at least 24 weeks. The levels of MMP-1, 2 and 9, TIMP-1 and 2, PIIINP (ELISA) and HA (RIA) were measured from serum collected the day of the biopsy and every 3 months during the treatment. METAVIR score was used. MMP-2 ($r=0.28$; $p<0.01$), TIMP-1 ($r=0.42$; $p<0.001$), HA ($r=0.50$; $p<0.001$) and PIIINP ($r=0.62$; $p<0.0001$) were positively correlated with Metavir fibrosis, whereas MMP-1 ($r=-0.34$; $r<0.001$) and MMP-2 ($r=-0.24$; $r<0.01$) were negatively correlated. By multivariate analysis, PIIINP and MMP-1 were independently associated with fibrosis. A score calculated by combining these two variables (logistic regression function) was able to discriminate F0/F1 from F2/F3/F4 with a sensitivity of 60% and a specificity of 91% (ROC curves). During treatment, MMP-1 significantly increase and PIIINP as well as combined score significantly decrease in virological responders but not in non responders. In

summary, non invasive markers might be useful for estimating liver fibrosis. IFN and ribavirin reduce liver fibrosis in virological responders by decreasing fibrogenesis as well as increasing fibrolysis.

34. Abstract Number: 112

ASSOCIATION OF HYPOGLYCEMIA AND PEG-INTERFERON IN HCV

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New therapy with PEG-interferon (IFN) +Ribavirin has been used to treat HCV infection. We noticed hypoglycemia (serum glucose <70mg/dl) developed during treatment with PEG-IFN, which has not been reported previously. The aim of this study is to assess the association of hypoglycemia and PEG-IFN treatment in HCV patients. **Methods & Results:** Blood glucose levels at 12 weeks after start of therapy in a total of 124 HCV patients including 61 treated with PEG-IFN alpha-2b (Peg Intron)+ Ribavirin and 63 patients with standard IFN alpha-2b + Ribavirin were compared to their baseline. The prevalence of hypoglycemia was approx 4 fold greater in patients treated with PEG-IFN and Ribavirin (30%) than patients with standard IFN+Ribavirin (8%) [P<0.05]. There was a significant decrease of blood glucose in patients with PEG-IFN and Ribavirin at 12 weeks in compared with baseline (78 + 2.4 vs. 93 + 2.9) [P < 0.001], while there was not a significant difference in patients with standard IFN + ribavirin. Age, gender, ALT, HCV genotype and liver histology were not associated with alteration in blood glucose. This is the first study to show that the HCV patients developed a very high prevalence of hypoglycemia (30%) and a significant decrease in blood glucose at 12 weeks after starting treatment with PEG-IFN + ribavirin compared to standard IFN+ribavirin. This may support previous findings suggesting that IFN-alpha significantly decrease insulin autoantibodies in HCV (Ismaeil, Hepatology; 2000 32: 369A). Further research is needed to evaluate the involved pathogenesis and clinical outcome due to the side effect of PEG-IFN.

35. Abstract Number: 34

NON-INVASIVE GRADING OF HEPATITIS C RELATED LIVER DISEASE: MICROBUBBLE-ENHANCED ULTRASOUND STUDIES

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Non-invasive assessment of the severity of liver disease is difficult. We evaluated hepatic vein arrival times (AT) of an ultrasound microbubble agent and carotid-delay times (CDT) in grading liver disease in patients with chronic hepatitis C (HCV) infection. 61 patients were studied. Grading of fibrosis (F) and inflammatory activity (NI) was carried out using the modified HAI (Ishak) system. Patients were divided into mild hepatitis, (F<3/6, NI<4/18); moderate/severe hepatitis, (F>2/6, NI>3/18) and cirrhosis, (F=6). Time-intensity curves of hepatic vein spectral Doppler signals and audio intensity from the carotid artery were analysed after an intravenous microbubble bolus. CDT was calculated as the difference between carotid and hepatic vein arrival times. There was a monotonic decrease in the mean ATs (1 s.d.) and CDTs (1 s.d.) for mild, moderate/severe hepatitis and cirrhosis: 50.5s (24.2), 33.6s (26.1), 14.8s (4.5) and 36.8s (29), 18.7s (22.6) and 5.8s (4.9) respectively (Kruskal Wallis, p<0.001). An AT<20s and CDT<10s was 100% sensitive for cirrhosis but only 69% and 72% specific respectively, as subjects with fibrosis sometimes showed early AT and CDT. 10 interferon-treated patients showed earlier arrival times than comparative untreated subjects. In summary, AT and CDT measurements hold promise in characterising HCV liver disease and are highly sensitive markers of cirrhosis. Treatment with interferon appears to prolong AT. This is important for disease monitoring and may be useful in assessing the efficacy of treatment regimes non-invasively and possibly

replace repeat liver biopsy in some situations.

36. Abstract Number: 5206

LOW RISK OF VERTICAL HEPATITIS C VIRUS (HCV) INFECTION IN A LARGE COHORT OF HUMAN IMMUNODEFICIENCY VIRUS (HIV)-SERONEGATIVE PREGNANT WOMEN

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Given that conflicting results are currently available on vertical HCV transmission, the aims of this study were to determine the prevalence of chronic HCV infection in a large cohort of HIV-negative pregnant women and to analyze the rate of vertical HCV transmission, assessing the possible related risk factors. We prospectively recruited 20,612 consecutive unselected pregnant women who were referred to the Obstetric Unit of the University Hospital Santa Cristina. HCV-RNA was assessed in blood samples from anti-HCV+ mothers at first and third trimester of pregnancy and from their newborns at birth and after 6,12,24, and 36 months. Viral load and genotype were determined to all viremic women at the time of delivery as well as to viremic infants. Antibodies to HCV was detected in 119 mothers (0.57%), whereas HCV-RNA tested positive in 67% of anti-HCV+ women (n=80). The median viral load of these viremic women, at time of delivery, was 335,300 copies per milliliter (range: 11,000 -2,625,200), and the vast majority of them had a low viral load. HCV genotyping revealed subtype 1 in 60 cases (75%). Only 2 newborns tested positive for HCV-RNA immediately after birth (transmission rate: 2.4%), remaining positive during the entire follow-up. These vertically-infected babies had the same HCV genotype (1b) that their respective mothers. In conclusion, vertical HCV transmission is an infrequent event among HIV-negative HCV-infected women and, in the present study, no apparent risk factor influencing the transmission rate was identified.

37. Abstract Number: 185

A 3-ARM RANDOMIZED STUDY EVALUATING THE EFFICACY OF TRIPLE THERAPY OF PEGYLATED OR RECOMBINANT INTERFERON ALPHA-2A 3 MU BOTH COMBINED WITH RIBAVIRIN AND AMANTADINE VERSUS DUAL THERAPY OF RECOMBINANT INTERFERON ALPHA-2A PLUS RIBAVIRIN IN NAIVE PATIENTS WITH CHRONIC HCV HEPATITIS

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We have previously shown that the addition of amantadine (AMA) to recombinant IFN alpha-2a was able to increase the efficacy of IFN monotherapy in pts with chronic hepatitis C (CHC). No data are available on naive pts to document whether triple therapy of AMA + ribavirin (RBV) and pegylated IFN (PEG IFN) (group A) or recombinant IFN alpha-2a (IFN)(group B) improves the success rate over dual therapy with recombinant IFN + RIBA. 354 naive pts with serologically and biopsy-proven CHC, persistently, elevated ALT and positive HCV RNA were randomized to a 3-arm multicenter trial, as follows: Group A: PEG IFN alpha-2a (Pegasys) 180 mcg sc qw +RBV 1-1,2g/qd + AMA 200 mg/qd Group B: IFN alpha-2a 3 MU tiw sc + RBV 1-1,2 g/qd +AMA 200 mg/qd Group 3: IFN alpha-2a 3 MU tiw sc + RBV 1-1,2 g/qd. Of 268 so far enrolled pts, 55.5% were male, mean age was 51 yrs (range 20-65): genotype 1 was found in 57.6% of cases. Severe fibrosis or cirrhosis were found in 23.3%. The treatments were well tolerated; no major safety

concerns were noted at the moment. One hundred and thirty pts have completed 3 mos therapy: at this time the percentages of pts with normal ALT levels were 51% in group A, 55% in group B, and 51% in group C. The rate of virological response was 54%, 49% and 42%, respectively. This study is ongoing and more data are needed to prove or disprove the value of triple therapy over the current standard therapy.

38. Abstract Number: 531

STUDY OF SEROLOGICAL MARKERS OF HBV IN POSTTRANSFUSIONAL HEPATITIS C

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The aim of this study was to assess the influence of past virus B infection in the development of postransfusional chronic hepatitis C (HCV). We enrolled 184 patients with postransfusional HCV (previous transfusion without other causes of hepatitis), older than 18 years, liver biopsy at least 4 years after transfusion. None of them had HBsAg. All sera were collected at the time of liver biopsy. HBsAg, HBcAc, HBsAc were assessed by ELISA (Abbott). Serum and liver tissue HBV-DNA were assessed by nested-PCR. Serum HCV-RNA levels were measured by Taqman (PE Applied Biosystems 7700). 36 patients with HCV present HBcAc with or without HBsAg (19.56%). No relation was found between age, gender, transfusion before 30 years, time to biopsy, alcohol or tobacco intake, blood cell count, biochemistry or ANOES. In patients with HCV and HBcAc histological fibrosis was significantly higher than in controls. 19 patients with HCV and HBcAc had fibrosis grade 3-4 (51.6%) against 33 (22.8%) in controls ($p=0.001$). DNA-HBV at serum was negative in all the cases and 20 controls. In liver biopsy DNA was negative in 5 patients analyzed. We did not find any difference in HCV-RNA levels between both groups. The prevalence of past HBV infection in patients with postransfusional HCV is 19.6%. HBcAc is associated with a higher level of fibrosis, so it seems to play a role in the development of the disease. The finding of markers of HBV was not associated with serum DNA neither differences in virus C replication.

39. Abstract Number: 639

RELATIONSHIP BETWEEN THE POPULATION OF HEPATIC STELLATE CELLS (HSC) AND LIVER IRON DEPOSIT IN CHRONIC HEPATITIS C

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Iron overload is related to more severe liver disease in chronic hepatitis C. Iron deposits occur mainly in Kupffer cells. Little is known about the role of liver iron deposits on HSC population in chronic hepatitis C. We studied the relationship between the population of activated and non-activated HSC and both the severity of liver disease and liver iron deposits in 49 patients with chronic hepatitis C. Eighteen had minimal/mild hepatitis, 25 moderate/severe hepatitis and 6 cirrhosis. Histological activity index (HAI) and fibrosis in liver biopsies were assessed using a score system from Knodell modified by Desmet. Iron deposit was assessed by Perls' staining. The population of activated HSC (aHSC) and non-activated HSC (nHSC) were determined by immunohistochemistry using antibodies to alpha-smooth muscle actin and glial fibrillary acid protein. A positive correlation was found between the number of either aHSC or nHSC and scores of HAI and fibrosis. Positive correlation was observed between scores of iron deposits and number of nHSC but not with the number of aHSC. Positive correlation was also found between iron deposits in hepatocytes and nHSC but not with aHSC. Higher number of both nHSC and aHSC was associated with iron deposits in Kupffer cells. In summary, the severity of liver disease is associated with HSC proliferation and activation. Iron deposits are related with HSC proliferation. When the deposits occur in Kupffer cells both proliferation

and activation are observed what could explain the more severe liver disease in chronic hepatitis C in this condition.

40. Abstract Number: 523

TEN-YEAR INCIDENCE OF HCV INFECTION IN NORTHERN ITALY AND FREQUENCY OF SPONTANEOUS VIRAL CLEARANCE

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Little is known about the incidence of HCV infection, and the frequency of spontaneous viral clearance in the general population is unknown. We conducted an epidemiological study in the two Apennine towns in northern Italy. ELISA III and RIBA III were used for anti-HCV determination in sera from the adult general population of Loiano and Monghidoro in 1986 and 1996. In 1999, anti-HCV positive (HCV-Ab+) subjects and sex- and age-matched controls were recalled. All HCV-Ab+ sera were tested with nested-RT-PCR. When negative in serum, HCV-RNA was also tested in leukocytes. Coincident sera of 1,646 adults (mean age in 1986, 43±0.39 years) were available. In 1986, 57 (3.46%) were HCV-Ab+. Eight new cases were recorded in 1996: adult incidence was 50.28 cases/100,000 inhabitants/year. 53/63 (84.12%) HCV-Ab+ sera were also HCV-RNA+. Genotype distribution was: 2a/2c, 44.4%; 1b, 27.0%; 2a/1b, 4.8%; 2a/1a, 4.8%; 1a, 3.2%; 1a/1b, 3.2% and unknown, 9.5%. HCV-Ab+ patients had higher ALT serum values with respect to controls (p<0.005), as did HCV-RNA-/HCV-Ab+ subjects with respect to HCV-RNA+/HCV-Ab+ ones (p<0.05), and subjects infected with genotype 1 with respect to those with genotype 2 (p<0.05). In 1999, 9/56 (16.1%) of the HCV-Ab+ subjects had spontaneously cleared HCV-Ab; 5/56 (8.9%) were also HCV-RNA- both in serum and leukocytes. In summary, in rural northern Italy, adult incidence is about 50 cases/100,000 inhabitants/year. Our findings suggest that as many as 10% of infected subjects may spontaneously clear HCV-Ab, but in some of them latent infection can persist in leukocytes.

41. Abstract Number: 5513

DOES NORMAL ALT EXCLUDE SEVERE HEPATIC FIBROSIS IN CHRONIC HCV PATIENTS?

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Background: It was suggested that chronic HCV patients with persistently normal ALT have minimal histological changes and may not require treatment. Aims: 1) Study the prevalence of normal ALT at the time of first evaluation in HCV patients. 2) Assess the significance of normal ALT in relation to hepatic histopathology. 198 untreated consecutive HCV patients, seen for the first time, were included. Demographic, laboratory and liver biopsy data were collected. Follow up ALTs for patients with normal ALT were collected to identify those with persistently normal values. 25/198 (12.7%) had normal ALT at the time of first evaluation. Patients with normal ALT had lower AST (P=0.0005), lower bilirubin (P=0.01), lower serum iron (P=0.003), lower body mass index (P=0.03), and less hepatic inflammatory activity (P=0.03). 52/173 (30%) patients with high ALT had severe hepatic fibrosis (stage III/IV) compared to 6/25 (24%) with normal ALT (P=0.5). Only 39% of normal ALT patients had persistently normal ALT. Results did not change comparing those with persistently normal ALT to patients with high ALT. In summary, 1) A single normal ALT at the time of first evaluation is common in chronic HCV patients but most did not have persistently normal values. 2) Patient with normal ALT had lower body mass index and hepatic inflammatory activity but

were equally as likely to have severe fibrosis suggesting that normal ALT in HCV patients should not preclude liver biopsy examination or therapy.

42. Abstract Number: 569

THE SIGNIFICANCE OF HEPATIC STEATOSIS (HS) IN CHRONIC HEPATITIS B AND C

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The aim of this study was to evaluate and compare the influence of HS on HBV- and HCV-related fibrosis in chronic hepatitis C (CHC) and B (CHB). Patients and methods: The consecutive 424 CHC (F/M: 193/231; age: 16-74, median 42 years) and 104 CHB patients (F/M: 29/75; age: 16-76, median 46 years) were studied. The liver specimens was evaluated by the Ishak's scoring system. Cirrhotic and alcoholic patients has been excluded. Progress of liver injury (classified as mild: staging score 0-2 or moderate/severe: staging score 3-5) was analysed in relation to the absence or presence (>1% of hepatocytes) of HS. The HS was more prevalent in CHC than CHB pts (217/424 vs. 34/104; p<0,001). No significant differences of HS frequency was found between mild and moderate/severe fibrosis groups (30.7% vs. 35.7%; p>0.6) of CHB pts in contrary to CHC pts (46.2% vs. 68.8% respectively; p<0.0002). Moreover, there was significant difference of the more extensive HS (>10% hepatocytes) frequency between mild and moderate/severe fibrosis groups (11.8% vs. 20.4%; p=0.04) of CHC patients and there was no similar difference in CHB patients (3.2% vs. 4.8%). In summary, HS was detected in more than 50% pts with CHC and seems to be an important factor in accelerating progress of liver injury in this group. Nearly 1/3 of CHB pts presented HS (predominantly not too extensive), which was not significantly associated to HBV-related fibrosis.

43. Abstract Number: 5167

EPIDEMIOLOGICAL FEATURES OF NEW DETECTED CASES OF HEPATITIS C AND SOURCE OF DIAGNOSIS IN A FRENCH GENERAL POPULATION

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Optimizing hepatitis C screening remains a priority. The aim of this study was to analyse, from a population-based registry, the link between patient characteristics and the source of diagnosis (general practice, private specialist practice, hospital, community clinic). Between 1994 and 1999, 1,508 new hepatitis C cases were diagnosed in the French Côte d'Or and Doubs areas. The following patient characteristics were analysed : age, sex, place of residence, alcohol consumption, contamination risk factors (high-risk lifestyle : intravenous drug use, sexual risk, tattooing, versus nosocomial risk and unknown risk factor). A polytomous logistic regression was used for the statistical analysis. Seven hundred and seventy-three patients (51 %) were diagnosed at a hospital versus 501 (33 %) in general practice, 146 (10 %) in private specialist practice and 88 (6 %) in a community clinic. Patients living in rural areas were more often diagnosed in general practice than in a hospital (OR= 1.64, p= 0.003). Patients under 40 were more often diagnosed in a community clinic (OR=2.09, p= 0.015) than in a hospital. High risk lifestyle patients were more often diagnosed in a community clinic (OR=2.47, p=0.003) or in general practice (OR=2.59, p<10⁻⁴) than in a

hospital. Alcohol consumers were more often diagnosed in a hospital than in the other 3 health care settings. This population-based study highlights the disparities in patient patterns based on the different health care settings. Screening should be intensified in general practices and community clinics, which are the foremost health care settings where high-risk lifestyle people may be reached.

44. Abstract Number: 565

DITTO-HCV EARLY VIRAL KINETICS REPORT - NOVEL DECLINE PATTERNS IN GEN 1 BUT NOT GEN 2-3 PATIENTS TREATED WITH PEG-INTERFERON-ALFA-2A AND RIBAVIRIN

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The DITTO-HCV EC funded project was designed to study the correlates of viral/host dynamics during treatment of HCV and explore a dynamically individualized therapy strategy. Methods: 300 naïve patients are currently receiving peginterferon-alfa-2a (40KD) and Ribavirin. Patients are randomized at week 6 to 5 treatment arms based on viral kinetics (Cobas Amplicor Monitor v2, Roche). 171 patients finished first month of treatment. Rapid viral response (RVR) was defined as a second slope faster than 0.3 log IU/ml/week. Mean first phase viral decline was 1.2, 2.6, 2.4 and 1.1 log IU/ml for genotypes 1, 2, 3 and 4, respectively. A bi-phasic viral decline pattern was observed in 92% of genotype-2-3 patients (N=60) but only in 44% of genotype-1 patients (N=104). Other patterns observed were: 1) delayed response after first week without decline (<0.5 log IU/ml) found in 18% of genotype-1 and 5% of genotype 2-3 patients; 2) Tri-phasic staircase decline, with a shoulder between day 1 and 3-15, found in 38% of genotype-1 and 3% of genotype-2-3 patients. All genotype-2-3 patients had RVR irrespective of the initial decline pattern. RVR was observed in all genotype-1 patients with bi-phasic decline, but only in 62% of tri-phasic decline and in 16% of delayed decline. In summary, almost all genotype 2-3 patients show the bi-phasic decline with rapid response. About half of genotype 1 patients do not have a simple bi-phasic decline, but nevertheless 70% of them are rapid responders. These results may be important in order to design of individualized therapies.

45. Abstract Number: 551

CLINICAL SIGNIFICANCE OF HCV CORE ANTIGEN, A NEW MARKER OF HCV INFECTION

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HCV core Ag can be detected and quantified in blood by means of an enzyme immunoassay (Total HCV core Ag assay, Ortho-Clinical Diagnostics). We studied the clinical significance of this marker, the intrinsic performance of the assay, and its practical use in the management of HCV-infected patients. The results showed that: (i) HCV core Ag and HCV RNA were significantly related in 392 clinical samples covering a wide range of HCV RNA loads ($r = 0.92$; $p < 0.0001$). 1 core Ag pg/ml was equivalent to approximately 8 000 HCV RNA IU/ml, with slight patient to patient variations. (ii) The dynamic range of quantification of the assay ranged from approximately 2 pg/ml to at least 250 pg/ml. HCV core Ag detection was in general negative in samples with less than 20 000 HCV RNA IU/ml. (iii) The specificity was 99.2% (95%CI: 94.3%-

100.0%). The within-run CVs ranged from 7.5% to 33.2%, the between-run CVs from 16.3% to 26.7%. (iv) In 40 patients receiving IFN-ribavirin treatment, total HCV core Ag quantification allowed the same classification as HCV RNA testing in 35 patients (87%). Discrepancies were related to lower sensitivity in the remaining 5 patients. (v) HCV core Ag was used to study viral kinetics during treatment : the first-phase (day 1) kinetics had a good agreement with HCV RNA, whereas the second-phase kinetics differed between the 2 assays, mostly due to lower sensitivity of core Ag detection. In summary, HCV core Ag quantification can be used as a reliable indirect marker of HCV replication in the clinical indications of viral load monitoring, but its use may be limited by the lower sensitivity compared to molecular biology-based assays.

46. Abstract Number: 451

EFFICACY AND SAFETY OF COMBINATION THERAPY WITH INTERFERON PLUS RIBAVIRIN IN HIV-INFECTED PATIENTS WITH CHRONIC HEPATITIS C

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Background: The interest of therapy for chronic hepatitis C (CHC) in HIV-infected persons is rising since end-stage liver disease is now a leading cause of morbi-mortality in this population. The combination of interferon (IFN) plus ribavirin (RBV) provides sustained response (SR) to nearly a half of HIV-neg subjects with CHC. However, information on the efficacy and safety of this therapy in HIV+ subjects is limited to few studies, having small population sizes. The efficacy and safety of IFN + RBV in HIV/HCV coinfecting individuals was examined in a multicenter, prospective trial beginning in Spain in Jan 2000. Patients were randomized to receive standard doses of IFN (3 mU tiw) and RBV (800 mg bid) or an induction period of 6 weeks with IFN 6 mU daily followed by IFN 3 mU tiw + RBV until completing 6 months of therapy. Only individuals with CD4 counts >350 cells/ul and HIV-RNA <5000 cop/ml were included in the trial. All were IFN-naive. A total of 111 subjects (82% male; mean age 36 years-old; 82% on HAART) were recruited in 14 centers participating in the trial. HCV genotype distribution was 1 (47%), 3 (38%) and 4 (15%). Mean HCV-RNA was 3,280,417; and 66% harboured >2 million cop/ml. HCV-RNA clearance (Roche, limit of detection 100 cop/ml) at month 6 (end-of-treatment response) was 29%. Relapses occurred in 23% of them within the next 6 months. Therefore, sustained response was limited to 22.3%. No differences between treatment arms were noticed. Of note, 70% of responders carried HCV-3. Treatment discontinuation due to adverse effects occurred in 12%. Although many subjects who reached SR showed HCV-RNA clearance at the 1st month on therapy, 50% of them showed a delayed virological response. No significant drops in the CD4 count nor increases in HIV-RNA were seen, even in subjects in which RBV was taking with AZT or d4T. RBV dose reduction due to anemia only was required in 4% of subjects. In summary, the combination of IFN+RBV is relatively well tolerated in HIV/HCV coinfecting patients. The rate of treatment discontinuation (12%) was similar to that seen in HIV-neg individuals, and unexpected side effects were not recorded. The relatively low rate of SR in our trial might be explained by the short duration of therapy (6 months) for patients carrying HCV-1 and/or the low dose of RBV (800 mg bid) in subjects with high weight. The lack of HCV-RNA clearance one month after beginning therapy does not preclude the attainment of response much later, and therefore can not be used as treatment decision time-point.

47. Abstract Number: 5277

GENDER DIFFERENCES IN HCV VIRAL LOAD AMONG METHADONE-MAINTAINED

PATIENTS

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The study is a prospective laboratory evaluation of both quantitative and qualitative HCV RNA in former heroin addicts in methadone maintenance treatment. 61 patients (23 females, 38 males) from the Adult Clinic of the New York Presbyterian Hospital and Weill Medical College of Cornell University were recruited. All were tested for anti-HCV antibodies (ELISA with confirmatory RIBA), and quantitative HCV RNA (bDNA technology, lower limit of detection, 521 IU/ml). Sixty patients were tested for qualitative HCV RNA (nested PCR technology, lower limit of detection, 4 IU/ml) followed by genotype analysis. Median age was 47 years; 50 patients (82%) were anti-HCV positive by ELISA, of which 74% (9 females, 28 males) were HCV RNA positive. Mean viral load was significantly higher in males than in females (2,253,424 IU/mL vs. 498,214 IU/mL respectively; Mann-Whitney U-test, $p < 0.05$). Qualitative HCV RNA was positive in 43 patients (13 females, 30 males), including 6 (4 females, 2 males) that had tested negative for quantitative HCV RNA. Unfavorable genotypes (type 1 or 4) were present in 90% of males, and 77% of females. In summary, methadone-maintained patients have a high prevalence of HCV infection; mean HCV viral load is significantly higher in males, and 90% are infected by unfavorable HCV genotypes 1 or 4.

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48. Abstract Number: 136

IMMUNOMODULATORY PROPERTIES OF PEGYLATED INTERFERONS: THE 40KD PEGYLATED IFN ALFA 2A HAS GREATER TH1 STIMULATORY ACTIVITY THAN THE 12 KD PEGYLATED IFN ALFA 2B

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Type I interferons (IFN) are a family of cytokines that have antiviral and immunostimulatory properties. Different Type I IFNs have different immunostimulatory effects, suggesting that minor changes can have profound effects on activity. Pegylated IFNs are modified IFNs which have improved pharmacodynamic properties and which are currently being used to treat chronic HCV. In trials with PEG-IFN monotherapy the 40kD pegylated IFN alfa 2a was more effective than the 12kD pegylated IFN alfa 2b but the two have similar effects when combined with ribavirin. We examined the commercially available pegylated IFNs in antiviral and Th1 induction assays. We used an in vitro antiviral assay with EMC virus and a fibroblast cell line and we measured induction of IFN inducible genes, including the IL-12 receptor that is critical for Th1 cell induction, in the T cell line KIT-2. We also studied the effects of the PEG-IFNs on generation of Th1 cells from naïve human T cells. The ratio of antiviral effects in fibroblasts: activity in KIT-2 cells was compared. For 12kD PEG-IFN alfa 2b the ratio was similar to parental IFN alfa 2b whereas PEG-IFN alfa 2a had enhanced effects in T cells. Hence 40kD PEG-IFN alfa 2a has a different interaction with the IFN receptor that leads to enhanced effects on T cells.

49. Abstract Number: 375

ABSENCE OF LONG TERM RELAPSE IN PATIENTS WITH A GOOD VIROLOGICAL RESPONSE AT 6 MONTHS AFTER TREATMENT FOR CHRONIC HEPATITIS C

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The complete and sustained response to treatment is defined as normal ALT and as serum HCV RNA clearance at 6 month after discontinuation of the treatment. The aim of this study was to determine whether late relapse could occur. 125 patients who had a complete and sustained response to interferon alpha alone or to interferon alpha - ribavirin combination have been included. ALT and serum HCV RNA were serially followed every 6 months. The mean follow-up was of 20 months after discontinuation of the treatment: 82 patients were followed for more than one year, 44 for more than 2 years, and 1 for more than 9 years. No virological relapse was observed for these 125 patients. Genotype distribution available was identical to at one of our reference Data Base (n=2027) . There was no statistical difference for sex . The mean age was 48 yrs. Histological lesions before treatment were staged using the METAVIR score. Necroticinflammation activity: mild (A1) 39%, moderate (A2) 49%, ; fibrosis: absent or mild (F0 or F1) 66%, moderate (F2) 14%, intense or cirrhosis (F3 or F4) 20%. In summary, the biochemical and virological good response observed 6 months after discontinuation of the treatment persist after on mean follow-up of 20 months. No virological relapse was observed for very prolonged periods This favorable evolution was even observed in patients with poor predictive factors of a response to treatment (more than 50 years, extensive fibrosis or cirrhosis, genotype 1b).

50. Abstract Number: 95

EFFECT OF ANTI - RETROVIRAL THERAPY ON LIVER-RELATED MORTALITY IN HIV/HCV COINFECTED PATIENTS

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Hepatitis C virus (HCV) infection takes a more progressive course in patients with concomitant HIV infection. Antiretroviral therapy has remarkably improved the prognosis of HIV but does not affect HCV replication. Thus, it remains unclear, whether HIV/HCV co-infected patients have a survival benefit. We retrospectively analyzed survival in 285 HCV/HIV co-infected patients, which had been followed since 1990. Total deaths and liver-related deaths were analysed by Kaplan-Meier statistics stratified with respect to highly active antiviral therapy (HAART) for the period I (1996-2000), and therapy with nucleoside analogues for the period II (1990-1995). In period I, overall 25 deaths and 10 liver-related deaths were observed. However, only two liver-related deaths were observed in the 94 patients who had received HAART ($p < 0.05$). Kaplan-Meier analysis confirmed a total survival benefit of HAART also for HIV/HCV co-infected patients (mean survival: 1749 versus 1585 days; $p = 0.041$). Furthermore, liver-related survival was significantly better in HAART-treated patients than in patients without HAART (mean survival: 1816 versus 1701 days; $p = 0.045$) In period II we also found significantly better total survival (2790 versus 1504 days; $p < 0.0001$) and liver-related survival (2969 versus 2050; $p < 0.0001$) in the patients on nucleoside analogues. However, probably due to emerging viral resistance this benefit was not maintained through period I. In conclusion, our survival analysis suggests that antiretroviral therapy significantly reduces total mortality also in HIV/HCV coinfecting patients, probably related to better preservation of immune functions. Therefore, antiretroviral therapy should not be withheld from HIV positive patients with concomitant hepatitis C.

51. Abstract Number: 409

TREATMENT OF CHRONIC HEPATITIS C WITH PEGYLATED INTERFERON PLUS RIBAVIRIN IN HIV-INFECTED PATIENTS

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Chronic hepatitis C (CHC) has become a significant problem in HIV+ patients since the prognosis of HIV disease has improved dramatically and, as a consequence, an increasing number of HCV-HIV coinfecting patient could develop an end-stage liver disease. Previous studies with pegylated interferon (Peg-IFN) plus ribavirin (RBV) in HIV negative patients suggest better efficacy than IFN plus RBV. The aim of this study is to assess the efficacy and tolerance of Peg-IFN alfa-2b (Peg Intron) plus RBV in HIV+ patients with CHC. A group of 65 HIV-infected patients with CHC was analyzed in a Spanish multicenter study. Almost all subjects had been previous IDUs. All were naive for IFN, and 95% were receiving HAART. All had CD4>300 and HIV RNA < 5000 cop/ml. HCV RNA > 800000 UI/ml was seen in 55%. Peg-IFN was administered sc weekly (150 mcg during three months and then 100 mcg until complete 6 months in genotype 2-3 and 12 months in genotypes 1-4). RBV was prescribed daily (400 mg BID). Mean age was 37 years old. Genotype distribution was HCV-1: 56%, HCV-3: 30%, HCV-4: 14%. End treatment response was achieved in 50% (83% genotype 3 and 25% genotypes 1-4). A breakthrough during treatment occurred in 22%. Adverse events leading to discontinuation occurred in 14% of patients. The more frequent adverse events were: flu-like syndrome, asthenia, depression, gastrointestinal symptoms and weight loss. Of note, 70% patients lost more than 10% of basal weight. No increases in plasma HIV-RNA were seen. In summary, the combination of Peg-IFN plus RBV is relatively well tolerated, and provides virological end treatment response in 50%. These results are promising and longer follow-up is warranted.

52. Abstract Number: 276

OPHTHALMOPATHY DUE TO TREATMENT WITH PEGYLATED ALPHA INTERFERON IN PATIENTS WITH CHRONIC HEPATITIS C

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Treatment with pegylated alpha-interferon (Peg-interferon) in patients with hepatitis –C has been associated with eye complications. The frequency of it as well as its clinical relevance has not been established as yet. Between June 2000 and June 2001 patients with hepatitis-C in one single institution were treated with Peg-interferon preparation (Peg-Intron, Peginterferon-alpha-2b, Essex Pharma) and evaluated ophthalmologically before, during and after treatment. We defined Peg-interferon induced ophthalmopathy if one of the following conditions occurred after treatment was started: reduction in visual field, retinitis, unsharpness of the papilla, cotton-wool focuses. 26 patients were treated. Ophthalmological data were available in 19. In 5/ 19 (26%) patients at least one of the conditions were found. Only one reported significant symptoms, i.e. reduction in visual field. In another treatment was discontinued after six weeks because the risk of a serious complication was judged to be high due to a one sided anophthalmus. Diabetes mellitus was present in this patient. Remarkably, retinitis and cotton-wool focuses disappeared after treatment had been stopped, and he viral eradication was obtained after only six weeks of treatment (4 months after end of therapy). In all other patients therapy was continued according to current standards, ophthalmological changes recovered when treatment was stopped. In summary, the incidence of ophthalmopathy due to treatment with Peg-interferon may underestimated. It is reversible and without clinical relevance in most cases. Yet, in some patients it may have impact on the course of therapy. Ophthalmological surveillance is recommended in patients treated with Peg-interferon.

53. Abstract Number: 677

INTERFERON ALONE VERSUS INTERFERON PLUS RIBAVIRIN IN THE TREATMENT OF PATIENTS WITH ACUTE HEPATITIS C: A PILOT STUDY

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Early treatment of acute hepatitis C may prevent progression to chronicity. In this study the efficacy of interferon (IFN) monotherapy versus interferon plus ribavirin combination therapy was evaluated in 17 acute hepatitis C patients with high ALT levels and persistent viremia after 3 months from onset. In all patients diagnosis of acute hepatitis C was based on a well-documented HCV seroconversion. Eleven patients were treated with IFN alone (5-3 MU tiw) and six patients received IFN plus ribavirin (800/1000 mg daily) for a total of 12 months. During therapy, patients were monthly monitored for blood count, transaminases and HCV RNA levels. Anti-HCV antibodies were measured every 6 months. All patients were followed for at least 6 months (range 6-38) after therapy discontinuation. Treatment was generally well-tolerated even if three patients reduced ribavirin therapy. At the end of therapy, 10/11 (91%) monotherapy and 5/6 (83%) combination therapy patients had normal ALT levels and undetectable HCV RNA. During follow-up, 2/10 (18%) and 1/5 (17%) patients relapsed after 1 and 5 months, respectively. Anti-HCV antibodies decreased in eight sustained responders. No correlation with response was found for genotype, pretreatment viral load or interval between acute infection and start of therapy. Our data show that early treatment prevents disease chronicity in most cases and that combination therapy does not improve the response rate. However, larger studies are needed to confirm these results and to verify if a 6-month IFN course is sufficient for HCV clearance in acute hepatitis C patients.

54. Abstract Number: 457

RAPID HCV RNA DECLINE AFTER DAILY 18 MU INTERFERON INDUCTION COMBINED WITH RIBAVIRIN AND AMANTADINE IN CHRONIC HCV PATIENTS

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The objective of this study is to study viral decline in HCV patients treated with high dose induction combination therapy during the first 6 weeks of therapy. 24 treatment-naïve patients with chronic hepatitis C received IFN according to the following schedule: week 1 and 2 8 hourly 6 MU, week 3 and 4 8 hourly 3 MU, week 5 and 6 12 hourly 3 MU, subsequently genotype non-1 patients were treated with 3 MU IFN daily uptill 26 weeks and genotype -1 patients until 52 weeks. All patients received also Ribavirin 1000-1200 mg and Amantadine 100 mg daily. Serum samples were obtained once weekly. HCV RNA levels were determined by bDNA (Bayer) or qualitative PCR (Roche). 15 patients had genotype non-1 (11 patients genotype 2 or 3, 4 patients genotype 4), 9 patients had genotype 1. Mean pretreatment viral load in genotype non-1 was 5.6 Log IU/ml vs. 5.6 log IU/ml in patients with genotype 1. The viral load decline after one week of treatment for patients with genotype non-1 and genotype 1 was 2.9 log IU/ml and 2.6 log IU/ml respectively. Between week 1 and 4 the viral load decline for patients with genotype non-1 and genotype 1 was 1.0 log IU/ml and 1.2 log IU/ml respectively. All patients (n=24) were HCV PCR negative at week 4. In conclusion, a rapid HCV RNA decline induced by high dose IFN induction therapy combined with Ribavirin and Amantadine in all patients independent of genotype. After 4 weeks of treatment all patients were HCV RNA negative.

55. Abstract Number: 5248

RIBAVIRIN/INTERFERON ALPHA-2B THERAPY IS VERY EFFECTIVE IN THE TREATMENT OF CHRONIC HEPATITIS C GENOTYPE 2&3 PATIENTS WHO HAVE FAILED TO RESPOND VIROLOGICALLY TO INTERFERON MONOTHERAPY

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Combination ribavirin and interferon (IFN) alpha 2b therapy is not currently approved for the treatment of chronic hepatitis C patients who were virologic non-responders (NR) to IFN monotherapy. We have recruited 200 patients who previously failed IFN monotherapy into a study to compare IFN induction followed by combination IFN/ribavirin therapy versus IFN/ribavirin therapy alone. Sixty four percent were NR to IFN monotherapy and 36% were responder/relapsers (RR). In this report, we focus on 24 patients in the induction group with HCV genotypes 2 and 3. Study design: Each patient received 10 MIU IFN alpha 2b daily for two weeks (induction phase) and then was started (week 0) on combination ribavirin/IFN for 52 weeks. All patients received a total IFN dose of 780 MIU and ribavirin at a daily dose (1000-12000 mg) based on body weight. They were followed for 78 weeks after commencement of combination therapy. Virologic response (VR) is defined as no detectable virus in blood samples by RT-PCR assay (lower limit of detection <100 copies/ml). V-ETR is defined as a VR at the end of treatment. Virologic sustained response (V-SR) is defined as no detectable virus 26 weeks after stopping therapy. The results showed that : (1) After induction (week 0), 86% of patients had no detectable virus (VR) in the blood. (2) The V-ETR in all patients was 83% (20/24), with 77% (10/13) in the NR group and 91% (10/11) in the RR group (p<0.01). (3) The V-SR in all patients was 75% (18/24), with 77% (10/13) in the NR group and 73% (8/11) in the RR group. (4) There were no breakthroughs and the dropout rate was between 9-15%. (5) The overall relapse rate approximated 8%. In summary, combination ribavirin/IFN alpha 2b therapy is effective with an approximately 75% V-SR in the subpopulation of chronic HCV patients with genotypes 2 and 3 who are virologic non-responders to IFN monotherapy. Thus, combination therapy should be offered to the subset of IFN non-responders with favorable genotypes.

56. Abstract Number: 5201

EFFICACY OF PEGYLATED (40KDA) IFN ALFA-2a (PEGASYS) PLUS RIBAVIRIN IN THE TREATMENT OF HEPATITIS C GENOTYPE 4 CHRONIC ACTIVE PATIENTS IN SAUDI ARABIA

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Background: Viral hepatitis C genotype 4, one of the most 'difficult to treat' HCV genotypes is also the most predominant in the Middle East. The aim of this study is to determine the efficacy of Peg-IFN alfa-2a plus Ribavirin in the treatment of Genotype 4 CAH patients. An open label, multicenter, trial in which 180 patients were enrolled and randomized into three treatment groups: A: Peg-IFN (180 mcg) qw plus Ribavirin (400 mgs bid); B: Peg-IFN (180 mcg) qw. C: Roferon (4.5MIU) tiw plus Ribavirin (400 mgs bid). Treatment is for 48 weeks, then 24 weeks follow-up. Patients are monitored biochemically, virologically and

histologically. Using the reduction of 2-log drop or HCV-RNA negativity at week 12 to predict response, our results show that 77% of group A ($p < 0.001$), 60% of group B ($p < 0.001$) and 22% of group C showed early viral clearance. Pegylated (40 KDA) IFN alfa-2a has a significantly higher response either as a monotherapy or in combination with Ribavirin for the treatment of Genotype 4 CAH cases.

57. Abstract Number: 624

COST-EFFECTIVENESS OF PEGINTERFERON ALPHA-2B PLUS RIBAVIRIN COMPARED WITH INTERFERON ALPHA-2B PLUS RIBAVIRIN FOR INITIAL TREATMENT OF CHRONIC HEPATITIS C

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Peginterferon alfa-2b (Peg Intron) plus ribavirin in previously untreated patients with chronic hepatitis C achieves the highest virological sustained response rates (SVR) but is expensive. The objective of this study is to assess the cost-effectiveness of peginterferon alfa-2b plus ribavirin. Cost-effectiveness is analyzed using a Markov-Model. Data sources used include randomised clinical trial data (Manns Lancet 2001), interview-based quality-of-life study, actual variable costs and reimbursement costs in the German health care system. The target population is patients with chronic hepatitis C with the time horizon being lifetime. Perspective: Societal. Interventions: Initial antiviral combination treatment with peginterferon alfa-2b plus ribavirin, compared with interferon alfa-2b plus ribavirin. Outcome Measures: Life expectancy, quality-adjusted life expectancy, lifetime costs, and incremental cost-effectiveness ratio in Euro per quality-adjusted life-year (QALY) gained. Results: Compared to no antiviral therapy, peginterferon plus fixed (54% SVR) or plus retrospective analysis of weight-based dosing of ribavirin (61% SVR) increased life expectancy by 4.2 and 4.7 years respectively. When compared to standard combination therapy, peginterferon plus fixed or plus weight-based dosing of ribavirin increased life expectancy by 0.5 and by 1.0 years with incremental cost-effectiveness ratios of 11,800 Euro/QALY and 6,600 Euro/QALY. Subgroup analyses by genotype, viral load, gender, and histology showed that peginterferon plus weight-based ribavirin remained cost-effective when compared to other well-accepted medical treatments. Peginterferon plus weight-based dosing of ribavirin was a more efficient use of resources than fixed dosing of ribavirin. In conclusion, Peginterferon plus ribavirin should prolong life, improve quality of life, and be cost-effective for the initial treatment of chronic hepatitis C. Grant Support: By Essex Pharma GmbH and Schering-Plough Corp.

58. Abstract Number: 657

DOES HEALTH-RELATED QUALITY OF LIFE REFLECT DISEASE SEVERITY IN CHRONIC HEPATITIS C PATIENTS?

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During the course of chronic hepatitis C (CHC), patients may experience health states ranging from mild CHC to decompensated cirrhosis, hepatocellular carcinoma, and liver transplantation that represent

variation in disease severity. The objective of this study is to assess whether patient-derived health-related quality of life (HRQOL) measurements for actual patients with CHC reflect the severity of their disease. Methods: Current clinical and histological health status was assessed and assigned to an ordinal severity of disease scale in 348 German patients with CHC who completed structured interviews using the following HRQOL methods: SF-36, EuroQoL (EQ-5D), transformed rating scale (RS), time trade-off (TTO), and standard gamble (SG). Spearman rank correlation coefficients (r) and multivariate stepwise regression were used in the statistical analysis. Results: Health state ranks were identical for SF-36 profiles and disease severity. Specifically, across all domains except pain patients with CHC were worse than German population controls and individuals with severe disease had worse SF-36 scores than those with less severe disease. Quality-of-life values based on RS ($r=0.28$; $p<0.001$) and EQ-5D ($r=0.20$; $p<0.001$) showed significant correlation with the severity of disease scale, but not with TTO and SG ($r<0.1$, $p>0.1$). RS and EQ-5D were highly correlated ($r=0.64$, $p<0.001$) suggesting robust results. In summary, this study suggests that severity of disease is reflected by SF-36, EQ-5D, and RS, but not by preference-based instruments as SG and TTO. In contrast to SF-36 profiles, the quality-of-life index values assessed through transformed RS or EQ-5D can be used in pharmacoeconomic studies in patients with chronic hepatitis C.

59. Abstract Number: 5532

CHARACTERISTICS AND OUTCOME OF AntiHCV POSITIVE SERUM HCV RNA NEGATIVE PATIENTS

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For individuals testing anti HCV positive but negative for serum HCV RNA diagnosis remains unclear. To investigate characteristics and outcome we include 180 patients with antiHCV positive and persistently normal ALT levels (3 measurements in 6 months). At inclusion demographics, liver test and serum HCV RNA were measured. Activity and fibrosis scores (Metavir) were measured in liver biopsy. Patients were controlled every 6 months during follow-up (46 ± 2 m). HCV RNA was positive (781 ± 79 IU) in 103 (57.2%) patients (Group 1) and negative in 77 (42.8%) patients (Group 2). Both groups showed differences in alcohol consumption (25.8 vs 13.1%; $P 0.03$) and serum levels of ALT (25 ± 0.6 vs 17 ± 0.7 IU; $P 0.0001$), AST (25 ± 0.6 vs 20 ± 0.5 IU; $P 0.0001$) and gammaglobulines (18 ± 0.5 vs 8 ± 0.4 %; $P 0.0002$). Liver biopsy show minimal or absent activity in 47.3% and 70% respectively (P : NS). Fibrosis was absent in 45.4 % and 80% (P : NS). During follow-up ALT serum levels remained in normal values 49 (52.2%) in group 1 and in 58 (87.9%) in group 2 ($P 0.0001$). No patient in group 2 showed HCV RNA positive during follow-up. Conclusions: Our results suggest that antiHCV positive HCV RNA negative patients have resolved infection.

60. Abstract Number: 55

LOW FERRITIN LEVELS AND BODY MASS INDEX ARE INDEPENDENT PREDICTORS OF PERSISTENTLY NORMAL ALT LEVELS IN HCV RNA POSITIVE SUBJECTS

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Chronic hepatitis, liver cirrhosis and liver cancer are known sequelae of chronic infection with HCV-virus. However, several HCV infected subjects have persistently normal serum aminotransferases levels (PNAL), and, in comparison to those with pathologic liver function tests (PLFT), show milder histological activity and a more benign long term prognosis. To identify factors associated with the PNAL stages, we have performed a retrospective observational study on a cohort of 1259 HCV infected patients, including

244 PNAL and 1015 PLFT. All patients, recruited at a single center over 8 years, were HCV-RNA positive and were defined as PNAL if LFT were persistently normal on quarterly determinations for at least 12 months. A logistic regression model (SPSS statistical package) was implemented to assess the independent association of the different variables with the PNAL or PLFT status. Prevalence of PNAL was 19,4%. Several variables differed significantly between PNAL and PLFT subjects: gender, BMI, age at diagnosis, serum ferritin levels, HCV-RNA levels and HCV genotype, 1a and 3a being less frequent among PNAL. When entered in a backward stepwise logistic regression model, only ferritin and BMI were independently associated with the PNAL status, and thus to the likelihood of a more benign course of the disease. Since both variables can be easily manipulated by non-pharmacological interventions, these observations are of relevance for the management of HCV infected patients.

61. Abstract Number: 396

MODELING THE HEPATITIS C VIRUS EPIDEMIC IN GREECE: IMPLICATIONS FOR THE FUTURE HEPATITIS C MORBIDITY AND MORTALITY

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Aim of this study is to estimate the number of patients in different stages of the chronic HCV infection, currently and in the near future, in Greece. Using the number of the prevalent chronic hepatitis C infections, data on the distribution of the various transmission groups and of their estimated year of HCV seroconversion, it was possible to reconstruct the infection curve. This analysis suggested that injecting drug users became the main transmission category after 1979. The natural history of the disease was simulated in age and sex specific subcohorts of newly infected subjects per year using transition probabilities from one disease stage to another. No treatment effect was applied and no newly acquired infections after 1998 were included. Based on an HCV prevalence of 1.0%, simulations up to 2020 demonstrated that the maximum increase in the number of patients in various stages, relative to 1998, will occur between 2008-2011 and is estimated to be 21.0% in cirrhosis cases, 31.3% in HCC cases, 26.8% in liver failure deaths and 38.2% in HCV-related HCC deaths. These results suggest that hepatitis C is a growing public health problem in Greece.

62. Abstract Number: 367

RANDOMIZED, CONTROLLED TRIAL WITH INTERFERON-ALPHA PLUS RIBAVIRIN WITH AND WITHOUT AMANTADINE SULPHATE IN PATIENTS WITH CHRONIC HEPATITIS C RELAPSING AFTER PREVIOUS SUCCESSFUL ANTIVIRAL TREATMENT

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Retreatment with standard regimens of interferon-alpha (IFN-alpha) and ribavirin in patients with chronic hepatitis C relapsing after a primary successful IFN-alpha treatment showed therapeutic efficacy with sustained virologic response rates of approximately 40-50%. The aims of the present trial were to evaluate efficacy and safety of IFN-alpha/ribavirin retreatment with and without amantadine sulphate in a cohort of 75

patients (46 males, 29 females, mean age 43 years) relapsing after primary successful antiviral treatment. Patients received IFN-alpha2b 5 MU daily for 4 weeks, 5 MU tiw for 20 weeks, followed by 3 MU tiw for additional 24 weeks in combination with ribavirin 1000-1200 mg/d (n=34) or with IFN-alpha2b/ribavirin plus amantadine sulphate 100 mg bid for 48 weeks (n=41). Treatment was discontinued in patients with detectable serum HCV-RNA after treatment week 24. After the 24 weeks follow-up period, an overall sustained virologic response was achieved in 53/75 (71%) patients. Slightly higher sustained virologic response rates were observed in patients receiving triple therapy compared with those retreated with IFN-alpha2b/ribavirin alone (73% vs. 68%). However, the observed difference between the two treatment arms was not statistically significant (p=n.s.). Irrespective of treatment, patients infected with HCV-genotype non-1 were more likely to respond to antiviral retreatment than patients infected with HCV-genotype 1 (89% vs. 60%; p=0.0017). In conclusion, the addition of amantadine sulphate to interferon/ribavirin retreatment did not lead to a significant improvement of antiviral efficacy. The observed relatively high overall sustained virologic response rate may be related to intensified interferon retreatment in combination with ribavirin compared with standard regimens.

63. Abstract Number: 215

RETREATMENT OF CHRONIC HEPATITIS C PATIENTS WITH PREVIOUS NON RESPONSE TO INTERFERON ALONE

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This study investigated the efficacy of interferon alpha daily induction versus induction plus ribavirin, in patients with chronic hepatitis C non responsive to prior therapy. Ninety eight nonresponders were assigned randomly to receive interferon-alpha six megaunit daily for one month followed by six every other day (group A) or in combination with ribavirin for one year (group B). HCV-RNA was performed at baseline, first month and then every three months. Follow-up lasted one year post treatment. Genotype one was predominant in both groups. Biochemical sustained response was higher in group B than in group A when comparing end of treatment and twelve months of follow-up (seventy one percent, forty eight versus fifty seven, thirty two respectively). The virological response rate was high in both groups at the end of treatment, but dropped to forty five percent (one year of follow-up) in group B compared to thirty in group A. All patients negative at the end of induction in group B achieved sustained response, while seven in group A became HCV-RNA positive in the post treatment. In summary, in chronic hepatitis C nonresponder patients both regimens lead to significantly increased end of treatment biochemical and virological response but dropped in both groups at the end of follow-up. A greater efficacy of the combination was observed in achieving complete sustained response and in decreasing the percentage of breakthrough and of relapse. The combination of high daily doses of interferon-alpha and ribavirin for one year appears to be a good therapy in previous nonresponders.

64. Abstract Number: 211

VITAMIN E IMPROVES IFN EFFICACY IN CHC PATIENTS INTOLERANT TO RIBAVIRIN

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Ribavirin and Interferon-alpha is the treatment of choice in patients with chronic hepatitis C (CHC); however, side effects or contraindications to ribavirin often result in dose reduction or cessation of therapy. We evaluated the efficacy of Vitamin E plus alpha-interferon in patients unable to receive Ribavirin. 46 CHC

patients (30 with hemolytic anemia during ribavirin therapy, 16 with contraindications to the compound) randomly received either recombinant IFN-alpha (5MU thrice/week) plus Vitamin E (900 mg/day) or recombinant IFN-alpha alone. Serum HCV-RNA, ALT and Vitamin E were determined periodically for 48 weeks. At baseline, the two groups were well matched for demographic and laboratory features. An end-of-treatment response was observed in 35% of patients receiving IFN-alpha plus Vitamin E and in 13% of those treated with monotherapy ($p < 0.001$, Fisher test). At the end of the six month follow-up, 95% of IFN+Vit E patients showed a sustained response compared to 33% of the monotherapy group. Plasma levels of alpha-tocopherol were increased two fold compared to basal values in patients receiving Vitamin E. We suggest that CHC patients unable to receive ribavirin, may benefit of the IFN-Vitamin E treatment. Although the intimate mechanism of the beneficial effect of vitamin E is not completely understood, it is likely that its antioxidant activity together with the reported immunological effect, may play a major role.

65. Abstract Number: 5184

ULTRASTRUCTURAL MODIFICATIONS IN HEPATOCYTES' MITOCHONDRIA OF 28 HIV-HCV COINFECTED

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Mitochondrial metabolic changes in HIV patients during antiretroviral therapy (HAART) probably are the main problem in industrialized country at the moment. Literature data regarding in-vivo mitochondrial alterations during HAART are still limited. METHODS: From December 2000 to September 2001 we performed liver biopsy for ultrastructural examination in 28 asymptomatic HIV/HCV+ patients (age 26-53 years), all were naive to HCV therapy and had more than 300/mm³ CD4+. This group was heterogeneous for HAART history, risk factors and viral infections age. We found a large kind of morphologic changes in hepatocytes' mitochondria in all biopsies. Mitochondrial hyperplasia was found only in 2 female. We found in 24/28 (87.5%) mitochondrial polymorphism. It was light in 17 (61%) but marked in the other 7 ones (25%). In 8 cases we found intramitochondrial inclusions (crystals) and in 3 we noticed reduction of matrical density. 7 presented decreased number of cristae with consequent homogeneous aspect of mitochondria. Only 3 were naive to HAART, but everyone presented intramitochondrial crystals, in two associated with light polymorphism and with reduction of cristae in the other one. 15 HIV/HCV+ were experienced in HAART (> 50 months of NRTI), but we didn't find worse or particular changes in these patients than the others. In summary, severe different morphological mitochondrial alterations may occur in these patients, but we have not found relationship between these changes and metabolic alterations during HAART.

66. Abstract Number: 178

STEATOSIS ACCELERATES FIBROSIS DEVELOPMENT OVER TIME IN HEPATITIS C VIRUS GENOTYPE 3 INFECTED PATIENTS

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Steatosis is a frequent histological finding in liver biopsies from patients with chronic hepatitis C virus (HCV) infection. Its cause and influence on disease progression is only partially understood. The aim of this study was to evaluate the impact of steatosis on fibrosis progression over time in relation to HCV genotype. Methods: We retrospectively analysed 98 patients who underwent dual liver biopsies prior to antiviral treatment. Median time between the biopsies was 6.3 years. Biopsy specimens were assessed for

necroinflammatory activity and fibrosis according to the Ishak protocol, as well as for steatosis (grade 0-3). Univariate analysis as well as multiple logistic regression analysis was used. Both prevalence and high grade (³ 2) of steatosis were strongly associated with HCV genotype 3, independent of gender, age, body mass index and alcohol use. Progressive fibrosis was more prevalent in patients whose initial biopsy showed steatosis. This effect was mainly seen in genotype 3 infected patients. Low-grade steatosis was observed in overweight patients with genotype non-3, but high-grade steatosis was associated with genotype 3, independent of body weight. In summary, our data confirm that steatosis is associated with HCV genotype 3 infection. Furthermore, steatosis was associated with progressive fibrosis over time, especially in genotype 3 patients. These data imply that hepatitis C patients should avoid overweight. Genotype 3 infected patients with steatosis ought to be selected for early antiviral therapy to avoid progressive fibrosis and to benefit from the relatively good treatment results in this group of patients.

67. Abstract Number: 5202

LOW FREQUENCY OF CIRRHOSIS IN HCV(1B)-INFECTION AFTER MORE THAN 20 YEARS

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From August 1978 until March 1979, 14 batches of anti-D immune globulin contaminated with hepatitis C virus genotype 1b from a single erythrocyte donor had been administered for prophylaxis of rhesus isoimmunization. All 2867 women involved had been recalled after January 12, 1979 for repeated screening of aminotransferases. They were prospectively followed in 9 regional centers. Now a cohort of 1018 women was reexamined by members of the EAST GERMAN HCV STUDY GROUP. Within 6 months after anti-D vaccination, 10% of these women had no evidence of disease, 90% acute hepatitis C (n=917) including 49% with symptomatic and 22% with icteric course. After 23 years, 85% of the 917 affected women still tested positive for anti-HCV and 55% for HCV RNA, among them 52% with chronic hepatitis C and 3% apparent HCV carriers. Only 0.4% had overt liver cirrhosis. Histology obtained in 44% of the viremic women showed hepatitis of minimal to moderate grade in 96%, portal fibrosis in 47% and septal fibrosis in 3% of the cases. In summary, formerly healthy young women, without hepatic comorbidity, may clear HCV (1b) infection in half of the cases or develop mild chronic hepatitis C with low risk of progression to cirrhosis within 23 years.

68. Abstract Number: 507

COST-EFFECTIVENESS OF TREATING HEPATITIS C IN INJECTING DRUG USERS

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As many as 96% of injection drug users have been exposed to hepatitis C virus. The decision to treat the infection is complicated by the usually slow and inconsistent progression of hepatitis C, the expense and side effects associated with therapy, concerns about treatment adherence and tolerability in drug users and risk for re-infection. The objective of this study is to compare no antiviral treatment to antiviral therapy in injection drug users. Design: Computer cohort simulation. Data Sources: Clinical trial data and published studies. Target Population: Selected hepatitis C-infected injection drug users with histologically advanced disease (i.e., moderate hepatitis or cirrhosis). Time Horizon: Lifetime. Perspective: Societal. Interventions: Initial antiviral combination treatment with interferon and ribavirin versus no antiviral therapy. Outcome measures: life expectancy, quality-adjusted life expectancy, lifetime costs. The results showed that over 20 years, antiviral therapy would decrease the absolute risk of cirrhosis by 13% and of liver related mortality by

7%. Antiviral treatment should increase life expectancy by 1.7 life years and 1.9 quality-adjusted life years. Over an average lifetime, antiviral therapy should be cost-effective with an incremental cost-effectiveness ratio of \$5,600 per discounted quality-adjusted life year gained compared to no antiviral therapy. Sensitivity Analysis: When varying age, gender, histology, genotype, and estimates of histologic progression or adherence, antiviral therapy remained beneficial and cost-effective. Conclusion: For selected injection drug users with histologically moderate chronic hepatitis C or cirrhosis, initial combination treatment should reduce the future risk of cirrhosis, prolong life, and be cost-effective. Sponsor: European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)

69. Abstract Number: 515

AGE AT INFECTION, GENDER AND VIRAL GENOTYPE AFFECT RATE OF FIBROSIS IN HEPATITIS C VIRUS INFECTION

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The rate of development of liver fibrosis in HCV infection varies between individuals. We sought factors increasing the risk of rapid fibrosis. HCV infected patients who had had a liver biopsy were identified. Biopsies were scored using the modified HAI (Ishak) and METAVIR systems. Duration of infection at biopsy was documented where known. Patients were treatment naïve at first biopsy. Fibrosis rate was defined as: fibrosis stage/ infection duration. Demographic features were examined for relationship to fibrosis rate using univariate and multivariate analysis. A subgroup of patients with 2 biopsies was examined to test the assumption that fibrosis progresses in a linear fashion. 917 patients were included. Male gender ($p=0.0001$), older age at infection ($p<0.0001$) and viral genotype 1 ($p=0.005$) were all associated with a rapid rate of fibrosis. On multiple linear regression they accounted for 29.5% of the variability in fibrosis rate ($R\text{ Squared}=0.295$). There was no significant relationship between alcohol and rate of fibrosis. METAVIR and Ishak scores were highly correlated ($R=0.935$, $p<0.0001$) with similar reproducibility ($Kappa=0.79$ Ishak, 0.93 METAVIR). In 138 patients who had 2 biopsies the predicted probability for an increase of 1 on the fibrosis score was too low to assess linearity. Treatment between biopsies led to a fall in fibrosis score ($p=0.027$) independent of viral clearance. In summary demographic features account for a minority of fibrosis rate variability. The Ishak and Metavir scoring systems are equivalent. Linearity of fibrosis progression cannot be usefully assessed in biopsies less than 7 years apart.

70. Abstract Number: 5054

'TOTAL HCV CORE ANTIGEN ASSAY': A NEW MARKER OF VIREMIA AND IT'S APPLICATION IN DIAGNOSIS

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The aim of this study is to evaluate the Ortho Total HCV Core Antigen Assay as a new marker of viremia and replication, in the presence or absence of anti-HCV antibodies. A multi-site study of over 1500 HCV patients, diagnosed by risk factor and RNA determination, and 567 non-HCV associated hepatitis patients, was carried out. HCV core antigen quantification and viral RNA load were measured at treatment baseline and during the course of IFN/Ribavirin therapy (Ortho Total HCV Core Antigen Assay ELISA and Amplicor ver. 2.0). The assay can be completed in 3 hrs. There was a 90.5% concordance between RNA copy and antigen (cut-off 1.5 pg/ml) at baseline of treatment, and a 100% agreement above 1,000-13,000 IU/ml. Sensitivity dilutions of genotypes 1-5 samples showed a 92-94% correspondence with PCR values. The

core antigen assay was linear to greater than 10 E(6) RNA copies/ml. Standard calibrator linearity was studied in 26 consecutive runs ($r(2) = 0.992$), and reproducibility of controls was within 10-12% CV. Performance of the assay on serum vs. plasma was excellent ($r(2) = 0.990$). In summary the Ortho Total HCV Core Antigen Assay provides a new indicator of HCV infection that is compatible with NAT, allows monitoring of HCV virus replication status, and may offer unique information on the disease state.

71. Abstract Number: 5235

TOTAL HCV CORE ANTIGEN ASSAY: A SURROGATE MARKER OF VIRAL REPLICATION AND IT'S USE IN MONITORING RESPONSE TO THERAPY

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The aim of this study is to evaluate the use of the Ortho Total HCV Core Antigen Assay ELISA (OCD, Raritan New Jersey, USA) to monitor response of patients receiving IFN/Ribavirin therapy. 272 patients, receiving various treatment regimens were evaluated for core antigen (log pg/ml) and RNA (log IU/ml, Roche Amplicor 2.0, NGI Superquant) at baseline and M1-M12 of treatment. At baseline, 100% concordance with RNA load was noted, and responders exhibited less than 32 pg/ml core (70%) and less than 2 E(6) RNA (78%). The PPV of the antigen assay was 82%, and the RNA 81%. The NPV of core and RNA values was 100%. In sustained responders, Core antigen and RNA correlated $r(2) = 0.779$ well. Therapeutic response was unbiased, and highly correlated in genotypes 1-5 (88.3%). Both core antigen and RNA levels were lower in SR; rapid decline of core antigen (5.2 log pg/ml) and RNA (5.1 log IU/ml) was seen after M1. Changes in both HCV RNA and Core antigen levels were equally indicative and predictive of response to IFN/Ribavirin treatment dynamics. In summary, HCV core antigen may provide an independent analyte to monitor patients receiving anti-viral therapy. The assay is compatible with NAT methods and may offer advantages in time and economics, as well as providing a new clinical tool

72. Abstract Number: 177

TRIPLE THERAPY WITH AMANTADINE SULPHATE PLUS RIBAVIRIN AND INTERFERON-ALPHA IN PREVIOUSLY UNTREATED PATIENTS WITH CHRONIC HEPATITIS C: RESULTS OF A DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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Controversial reports exist on the usefulness of the application of amantadine as an additional regime in the treatment of patients with chronic hepatitis C. We therefore conducted a study on 400 previously untreated patients with histologically proven chronic hepatitis C receiving amantadine sulphate (100 mg bid, group 1) or a matched placebo (group 2) together with IFNa induction therapy plus ribavirin (1000-1200 mg/day) for 48 weeks. The two groups showed similar demographic, biochemical and virological baseline characteristics. IFNa and ribavirin dose reduction was necessary because of side effects in 15% and 16%, and 41% and 33% of the amantadine and placebo group, respectively. Amantadine/placebo dose was reduced in 1% and 0.5%. Based on intention-to-treat analysis, a sustained virological response after 24 weeks follow-up was observed in 52% of the amantadine group and in 43% of the placebo group ($p = 0.055$). The on treatment response rate at week 24 was significantly higher in the amantadine group (70%) as

compared to the placebo group (59%) (p=0.02). Baseline factors significantly associated with sustained response were HCV genotype (p=0.0001), GGT (p=0.001), ALT (p=0.008), age (p=0.004), fibrosis stage > 2 (p=0.015) and body weight (p=0.05). In summary, triple therapy with amantadine plus IFN α induction and ribavirin lead to a significant higher on treatment response and also slightly improved sustained virological response rate (p=0.055) when compared to combination therapy with interferon alpha-2a induction plus ribavirin. Thus, amantadine seems to have an additional antiviral effect in patients with chronic hepatitis C.

73. Abstract Number: 481

TREATMENT WITH 40kd PEGYLATED (PEG)-INTERFERON (IFN) ALFA2a MAY OVERCOME PRIMARY IFN-RESISTANCE IN PATIENTS WITH CHRONIC HEPATITIS C (GENOTYPE 1)

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The objective of this study is to study the response to an IFN test dose as a predictor of outcome of standard IFN/ribavirin therapy (Jessner et al, Lancet 2001). In this study we determined whether response to PEG-IFN α 2a/ribavirin can be similarly predicted.

22 pts with chronic hepatitis due to HCV genotype 1 (m:14, f:8; median age: 44 years [range:30-63]) were studied. To identify IFN-resistance, the decrease in viral load following a test dose (9 MU IFN α 2a; Roferon, Roche, Basel, CH) given 7 days (D-7) before starting treatment with 180 microg PEG(40kd)-IFN α 2a/week (Roche, CH) for 2 weeks (D0 to 13) was measured. Thereafter 800 mg ribavirin/d was added. The total treatment duration was 50 weeks. Viral load was determined by the Cobas Amplicor Monitor HCV Test, v2.0 (Roche Diagnostic Systems, USA). Endpoints were the qualitative HCV-RNA status after 6 months of treatment, at end of treatment and 6 months thereafter. The predictive value of the cutoff of the 24h test dose response (calculated from ROCs) separating responders and nonresponders to standard IFN/ribavirin (decrease in viral load of <0.8 log) was studied in patients on PEG-IFN α 2a/ribavirin. In the standard IFN/ribavirin group a decrease in viral load of <0.8 log predicted nonresponse with 100 percent specificity (15 of 15 pts). In contrast, 12 pts on PEG(40kd)-IFN α 2a were below this cut off but 6 of them became virologic responders (standard vs. PEG-IFN: p=0.003). In summary, patients with predicted poor response to standard-IFN/ribavirin therapy achieve a virologic response on PEG-IFN α 2a/ribavirin therapy. Thus, PEG-IFN α 2a may overcome IFN-resistance in HCV-genotype 1 patients.

74. Abstract Number: 521

HIGH VIRAL RESPONSE RATES IN PREVIOUS NONRESPONDER PATIENTS WITH HEPATITIS C TREATED WITH DAILY DOSING OF CONSENSUS INTERFERON AND RIBAVIRIN

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Retreatment of non-responders with interferon alfa and ribavirin results in sustained response rates of only about 7%. Recent studies have shown improved response rates using consensus interferon (CIFN) as monotherapy in non-responders. In this study, the efficacy of CIFN induction therapy followed by CIFN/ribavirin treatment in non-responders is evaluated. 103 patients of a total of 120 patients have so far been included. All patients had elevated ALT - values and were viremic, 91% had genotype 1. Patients are treated with CIFN 18 ug QD for 4 weeks, followed by 9 ug QD for 8 weeks or with CIFN 27 ug QD for 4 weeks, followed by 8 weeks CIFN 18 ug QD. Thereafter, treatment is continued in all treatment groups with CIFN 9 ug QD and ribavirin for 36 weeks. Results show that after the initial 12 weeks of CIFN monotherapy,

a negative HCV RNA is observed in 42% of patients in the CIFN 18/9 ug group and in 51% in the CIFN 27/18 ug group. After 24 weeks of CIFN/ ribavirin combination therapy, a negative PCR is observed in 54% in the CIFN 18/9 ug + ribavirin group, and in 72% of the CIFN 27/18 ug + ribavirin group. Due to side effects CIFN had to be reduced in 14% and discontinued in 5% of patients. CIFN induction therapy + ribavirin thus shows promising response rates in non-reponders. If these response rates will translate into corresponding sustained response rates, an effective treatment modality will be in place for this difficult-to-treat patient group.

75. Abstract Number: 323

SERUM BIOCHEMICAL MARKERS OF LIVER FIBROSIS IN HUMAN IMMUNODEFICIENCY VIRUS (HIV) AND HEPATITIS C VIRUS (HCV)-COINFECTED PATIENTS

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Liver biopsy is the gold standard for assessing fibrosis in HCV-infected patients. In these patients, we have validated a fibrosis index including age, gender, and biochemical markers (bilirubin, gamma-glutamyl-transpeptidase [GGT], alpha2-macroglobulin, apolipoprotein A1 [apoA1], and haptoglobin); however, its utility in HIV-coinfected patients is unknown. The objectives of this study are to determine the: 1) utility of this index in HIV/HCV-coinfected patients; and 2) incremental value of the CD4 count and HIV load. Methods: 131 consecutive, coinfecting patients with a liver biopsy, and serum stored within 6 months were included. The 5-marker index was applied for the diagnosis of F2-F4 fibrosis. An HIV-specific index including the CD4 count and HIV load was constructed using multivariate logistic regression analysis. The diagnostic values of these indices were compared using areas under ROC curves (AUC). The prevalence of F2-F4 fibrosis was 44% (n=58). By multivariate analysis, the most informative markers were alpha2-macroglobulin (P<0.0001), GGT (P=0.05), apoA1 (P=0.06), and gender (P=0.02), whereas the CD4 count and HIV load were not independently predictive of F2-F4 fibrosis. For the diagnosis of F2-F4 fibrosis, the AUC of the 5-marker index was 0.802 +/- 0.040. A high positive predictive value (>90% certainty of a diagnosis of F2-F4 fibrosis) was obtained for scores from 0.70 to 1.00, and a high negative predictive value (>90%) for scores from zero to 0.10. The AUC of the HIV-specific index did not differ significantly from the 5-marker index (P=0.15). In conclusion, an index including five biochemical markers accurately predicts significant fibrosis in patients with HIV/HCV coinfection.

76. Abstract Number: 458

ANALYSIS OF THE IMMUNOMODULATORY ACTIVITY OF LEVOPRIN, A SECOND GENERATION RIBAVIRIN ANALOGUE, ON T-CELL RESPONSES TO HEPATITIS C VIRUS

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Ribavirin is an essential component of current combination therapy for chronic hepatitis C, which acts primarily by modulating HCV-specific T-cell reactivity. Levoprin, an L-enantiomer of Ribavirin, is a new compound, which lacks Ribavirin-associated toxicity. Aim: To compare the effects of Levoprin and Ribavirin on HCV-specific T-cell reactivity. PBMC from 19 HCV RNA+ patients were cultured with recombinant HCV proteins (core, NS3, NS4) or tetanus toxoid (TT) alone and in the presence of Levoprin or Ribavirin (0.1,

0.5, 1.25, 2.5, 5.0 and 10.0 mg/L). PBMC from healthy controls were also used to compare the effects on T-cell responses to a recall antigen (TT). T-cell responses were analysed by T-cell proliferation; Elispot assays for IFN-gamma or IL-10 producing T-cells; cytokine mRNA expression in HCV-stimulated PBMC using TaqMan real time PCR. Levovirin and Ribavirin increased the number of IFN-gamma producing CD4 T-cells (peak effect at 0.5 mg/L) in response to HCV proteins, significantly higher than without either drug ($p=0.007$). Similar effects were observed for CD8 IFN-gamma T-cells. Both compounds accelerated the kinetics of IFN-gamma gene expression, with higher mRNA levels induced by Levovirin than Ribavirin, indicating its greater activity on IFN-gamma gene transcription. In contrast, at 0.5 mg/L, Levovirin and Ribavirin markedly reduced the number of IL-10 producing CD4 T-cells. At high concentrations (above 2.5 mg/L) both compounds significantly increased the number of HCV-specific IL-10 producing CD4 T-cells ($P<0.01$). In summary, these results demonstrate that Levovirin promotes Th1 profile of T-cell responses to HCV and may have greater immunomodulatory activity than Ribavirin.

77. Abstract Number: 583

LIVER TRANSPLANTATION IN HIV-HCV COINFECTED PATIENTS. NEW INDICATION AND PRELIMINARY EXPERIENCE

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HIV infection is considered as a contraindication for liver transplantation (LT). The prognosis of HIV infection has dramatically improved with antiretroviral treatment. Many of these patients have severe life-threatening HCV liver disease. Aim: Evaluate the feasibility of LT in HIV/HCV coinfecting patients. Six patients (5 M, 1 F) mean age 39 years underwent LT from December 1999 to October 2001. All patients have Child C cirrhosis and controlled HIV replication. HIV and HCV serum viral load were performed before and after LT, liver biopsy was performed at 6, 12 and 24 months post-LT. Immunosuppression was a combination of Tacrolimus and steroids. Results: 3 patients received a domino graft (from a donor transplanted for familial amyloidotic polyneuropathy); 2 a living related donor graft and 1 a cadaver graft. All patients are alive, mean follow-up 9 months (2-23). Protease inhibitors and tacrolimus interaction was responsible for acute rejection by low tacrolimus level in 1 and for toxic levels of tacrolimus in 1. After LT, all patients but one have undetectable or low level of HIV RNA, and all have high level of serum HCV RNA with hepatitis. One patient developed an unexplained episode of jaundice. One developed a severe chronic hepatitis C requiring combination therapy of interferon plus ribavirin, which was successful (HCV RNA negative). Significant improvement of quality of life and gain of weight was observed in 4 patients. Conclusion: Liver transplantation in HIV-HCV coinfecting patients is feasible but require a cautious monitoring of HCV reinfection, and of drug interactions.