

2003 EASL Conference Summary of Abstracts on Hepatitis C

This summary contains selected abstracts on hepatitis C, HIV/HCV coinfection and HBV/HCV from the EASL Conference that was to be held in Istanbul, Turkey, but was cancelled due to the war in Iraq. EASL 2003 has been rescheduled for July 3-6, 2003 in Geneva, Switzerland.



Print this page

1. Impact of Hepatitis C-Associated Autoantibodies (AABs) on the Liver Pathology and the Response to Antiviral Therapy
2. Effect of Antiviral Treatment of Evolution of Liver Steatosis in Patients with Chronic Hepatitis C: Evidence for a Role of HCV Genotype 3 in Steatosis
3. Psychological Impact of Chronic Hepatitis C Diagnosis: Comparison with Other Stressful Life Events
4. Hepatitis C Infection in the General Urban Population: Prevalence and Spectrum of Disease
5. Time to Development of Chronic Liver Diseases in Genotype 1 Dominant Population of Chronic Hepatitis C Virus Infection
6. Retreatment with High Vs. Conventional Doses of Consensus Interferon and Ribavirin of Patients with Non-Response or Relapse After Previous Treatment with Alpha-Interferon
7. Predictive Value of Early Virological Reduction (EVR) in the Response at 24 weeks (W) of HCV Treatment with Peg-Interferon (PEG-IFN) & Ribavirine (RBV) in HIV-Infected Patients (P)
8. Long Term Follow-Up of Glycyrrhizin Therapy in Patients with Chronic Hepatitis C and Non-Response to Interferon: Meta-Analysis of Individual Patient Data
9. Biochemical and Histological Hepatic Disease Activity in Cryoglobulinemic Patients
10. Treatment of Chronic Hepatitis B/C Coinfected Patients with Consensus Interferon/Ribavirin/Lamivudine Triple Therapy
11. Histological Damage in Liver Biopsy Specimens from 492 HIV-HCV Coinfected Patients: A European Collaborative Study
12. Presence of Multiple HCV Genotypes and Response to Interferon Therapy
13. Impact of Liver Histology and Relationship with Response to Combination Therapy of Occult Hepatitis B Virus Infection in Patients with Chronic Hepatitis C
14. Pathological Evolution of HCV-Healthy Carriers: A Multivariate Analysis
15. Pharmacokinetics of Pegasys Compared to Peg-Intron in Treatment-Naïve Patients with Chronic Hepatitis C
16. Pegasys (pegylated interferon alfa-2A) or Roferon A (standard interferon alfa-2a) Plus Ribavirin Plus Amantadine in HCV Treatment-Naïve Patients
17. Patients with High HCV Viral Load, Genotype 1 and Cirrhosis May Require More than 48 Weeks Combination Therapy with Pegasys + Copegus
18. Pegasys + Copegus Is Cost-Effective Compared with Rebetrone in Treatment-Naïve Patients, Regardless of HCV Genotype
19. Therapy with Pegasys + Ribavirin + Amantadine Shows Significantly Better 6-month Virological Response Than Treatment with Roferon + Ribavirin + Amantadine in Non Responders Previously Treated with Roferon + Ribavirin
20. Pegasys (peginterferon alfa-2a) Plus Amantadine May Be Effective Alternative Regimen for Patients Intolerant to Ribavirin
21. After 24 Weeks of Pegasys/Ribavirin Combination Treatment, Pegasys Monotherapy for 22 Weeks Results in Higher Rate of Virological Breakthrough Than Continued Combination Therapy
22. Cytokine Levels in Peripheral Blood of Chronic Hepatitis C (CHC) Patients Pre-And-Post-Treatment with Peg-Interferon Alfa-2B and Ribavirin

23. [The Influence of Analytic Time Horizon and Treatment Management Algorithms on The Cost of Peginterferon Alfa-2B Plus Ribavirin Therapy for Chronic Hepatitis C](#)
24. [Chronic Hepatitis C \(CH-C\) Genotype 1: An Independent, Multicenter RCT Comparing Peg-IFN Alfa-2B 12KD Plus Ribavirin \(RBV\) and IFN Alfa-2B Plus \(RBV\) in Naïve Patients](#)
25. [Evaluating Rapid Virological Response Reduces Ribavirin and Peginterferon Alfa-2B Treatment Costs for Chronic Hepatitis C in the United Kingdom](#)
26. [Is Peginterferon Alfa-2B Plus Ribavirin Cost-Effective for Treating Chronic Hepatitis C in the United Kingdom?](#)
27. [Efficacy of Pegylated Interferon Alpha-2B in Combination with Ribavirin in Patients with Chronic Hepatitis C Non-Responders to Previous Treatment](#)
28. [Controlled Trial with Pegylated Interferon-Alpha 2B Plus Ribavirin Retreatment in Patients with Chronic Hepatitis C Not Responding to a Previous Antiviral Treatment with Standard Interferons Combined with Ribavirin](#)
29. [Short Treatment \(14 Weeks\) with Pegylated Interferon Alpha-2B and Ribavirin for the treatment of Hepatitis C Genotype 2/3 Infection](#)
30. [Treatment of Chronic Hepatitis C in HIV Infected Patients \(PTS\) with Pegylated Interferon Alpha 2B \(PEG-IFN\) Plus Ribavirin \(RBV\) Versus Pegylated Interferon Alpha 2B](#)
31. [BITRIPEG Study: Triple Therapy with Peginterferon Alfa-2B Plus Ribavirin Plus Amantadine Versus Standard Therapy in Non-Responders – An Interim Analysis](#)
32. [Interferon Sensitivity in Chronic Hepatitis C Virus Genotype 3 Infection](#)
33. [Early Virologic Response \(EVR\) at Week 8 is More Predictive of Sustained Response \(SR\) to Pegylated Combination Therapy Than at Week 12](#)
34. [The Impact of Steatosis on Baseline Characteristics and End of Treatment Response for Chronic Hepatitis \(C\) Genotype 4 Patients Treated with Interferon](#)
35. [Preference-Based Quality-of-Life Values in Patients with Chronic Hepatitis C: Results from the German Hepatitis C Quality-of-Life Study](#)
36. [Effectiveness and Cost-Effectiveness of Initial Antiviral Treatment in Patients with Chronic Hepatitis C. A German Health Technology Assessment and Decision Analysis Commissioned by the German Federal Ministry of Health](#)
37. [Observational Study of Patients Treated for Chronic Hepatitis C in France](#)
38. [Is Treatment of Chronic Hepatitis C in Patients Under Methadone Maintenance Feasible? A Prospective; Controlled Study](#)
39. [High SVR Rate in HCV PTS with Normal or Increased ALT: A Controlled Study with IFN Alpha 2B and Ribavirin](#)
40. [Controlled Study of Interferon A-2B \(IFN\) Plus Ribavirin \(RIB\) in Patients with Chronic Hepatitis C \(CHC\) ‘Non-Responders’ to IFN](#)
41. [Immunological, Virological and Clinical Long-Term Follow-up After Interferon Therapy of Acute Hepatitis C Infection](#)
42. [Predictive Value of Early HCV RNA Quantification for Sustained Response in Non Responders Receiving Daily Interferon and Ribavirin Therapy](#)
43. [Compliance and Effect of Treatment for Chronic Hepatitis C \(CHC\) in Intravenous Drug Users \(IVDUS\)](#)
44. [Liver Fibrosis Regresses Better with Peginterferon Alpha and Ursodeoxycholic Acid Treatment than Spontaneous Recovery](#)
45. [A Randomized Controlled Trial of Pegylated-Interferon Alpha-2B + Ribavirin Vs. Interferon Alpha-2B + Ribavirin in HIV Co-Infected Patients](#)
46. [High Risk of Mitochondriopathy in HIV/HCV Co-Infected Patients Under Concomitant DDI/D4T and Interferon \(Standard or Pegylated IFN\)/Ribavirin Treatments](#)
47. [Preliminary Results of Naïve Combination Therapy with 12KA PEG-IFN a-2B and Ribavirin in Recurrent Hepatitis C After Liver Transplant \(LT\)](#)
48. [Treatment of Naïve Hepatitis C Recurrence \(HCV-R\) in Liver Transplant Recipients with Pegylated Interferon Alpha-2B and Ribavirin](#)
49. [Preliminary Treatment Results of Pegylated Interferon Alpha 2B and Ribavirin in Liver Transplant Recipients with Recurrent Hepatitis C Virus Nonresponsive to Interferon Alpha2B and Ribavirin](#)

- [50. Pilot Study of Treatment with Pegylated Interferon and Ribavirin in Liver Transplant Recipients with Hepatitis C Infection](#)
- [51. Predictors of Virologic Response in Combination Therapy with Interferon \(IFN\) Alfa 2B Plus Ribavirin of Recurrent Hepatitis C After Liver Transplantation \(LT\)](#)
- [52. Does Interferon Treatment of Chronic Hepatitis C Affect The Long Term Clinical Course After Renal Transplantation?](#)

IMPACT OF HEPATITIS C-ASSOCIATED AUTOANTIBODIES (AABs) ON THE LIVER PATHOLOGY AND THE RESPONSE TO ANTIVIRAL THERAPY

J. Massard , ¹C. Johanet, ²P. Bedossa, ³T. Poynard, ¹C. Buffet, ⁴V. Di Martino, ¹

**Presenting Author, ¹Hepatogastroenterology Unit, GH Pitie-Salpetriere, Paris, ²Dept Of Immunology, Hopital Saint-Antoine, Paris, ³Dept Of Pathology, GH Bicetre, Le Kremlin-Bicetre, ⁴Hepatogastroenterology Unit, GH Bicetre, Le Kremlin-Bicetre, France*

Aim: This work was to evaluate the relationship between AABs and liver damage and the response to antiviral therapy in HCV-infected patients.

Patients and methods: 439 patients with histologically-proven CHC consecutively seen between 1999 and 2001 and tested for AABs were considered for this study. Relationship between AABs, necroinflammation, steatosis, fibrosis, fibrosis progression rate (FPR), and response to anti-HCV therapy were studied through multivariate analyses taking into account alcohol consumption, age, gender, BMI, and HCV-genotype.

Results: The overall prevalence of AABs was 18% (10% antinuclear, 2.3% anti-LKM1, 7.7% anti-SM). Through multivariate analyses, 1) a high activity score (A2 or A3 according to the METAVIR scoring system) was independently associated with marked steatosis (OR=1.96, p=0.020) and presence of AABs (OR=1.92, p=0.016), 2) a steatosis >10% was associated with age >40 yrs (OR=1.97, p=0.034), HCV-genotype 3 (OR=3.27, p=0.002), BMI>27kg/m² (OR=2.54, p=0.002), and absence of AABs (OR=0.47, p=0.031). 3) factors associated with marked fibrosis (METAVIR F2 to F4) were age >40 yrs (OR=2.11, p=0.002), alcohol consumption (OR=3.67, p=0.0004), activity score A2A3 (OR=6.71, p<0.0001) and steatosis >10% (OR=1.60, p=0.049). Presence of AABs was associated neither with fibrosis score nor with FPR. In treated patients, end-of-treatment response (EOT-R) and sustained virological response (SVR) were observed in 34% and 22%, respectively. Presence or absence of AABs did not influence EOT-R or SVR.

Conclusions: In CHC, patients with detectable AABs have more marked necroinflammatory lesions and less severe steatosis. These results suggest the involvement of Th2 immune response on both necroinflammation and inhibition of steatogenesis.

EFFECT OF ANTIVIRAL TREATMENT ON EVOLUTION OF LIVER STEATOSIS IN PATIENTS WITH CHRONIC HEPATITIS C: EVIDENCE FOR A ROLE OF HCV GENOTYPE 3 IN STEATOSIS

L. Castera , ¹C. Hezode, ²F. Roudot-Thoraval, ³I. Lonjon, ²E.S. Zafrani, ⁴J.M. Pawlotsky, ¹D. Dhumeaux, ²

**Presenting Author, ¹Virology (EA 3489), Henri Mondor Hospital, University Paris XII, Creteil, France ²Hepatology And Gastroenterology, Henri Mondor Hospital, University Paris XII, Creteil, France ³Public Health, Henri Mondor Hospital, University Paris XII, Creteil, France ⁴Pathology, Henri Mondor Hospital, University Paris XII, Creteil, France*

Aim: To study the relationship between steatosis evolution and HCV clearance after antiviral treatment in patients with chronic hepatitis C and paired liver biopsies.

Methods: 125 naïve patients (HBsAg and anti-HIV negative, 34 with HCV genotype 3; 91 with HCV

genotypes non 3) were selected according to the following criteria: (a) the presence of steatosis at initial biopsy; (b) treatment with interferon-alpha (3 to 6 MU thrice weekly for 6 to 12 months) between the 2 biopsies; (c) BMI < 28 kg/m²; (d) absence of excessive alcohol intake. Steatosis evolution was examined by comparing grades between the 2 biopsies.

Results: After antiviral treatment, steatosis improved in 34% of cases, was stable in 51% and worsened in 15%. Steatosis improvement was significantly more frequent in patients with a sustained virological response (SVR) than in non responders (NR) (60% vs 30%; $p < 0.03$). This was also the case in genotype 3 patients (88% vs 19%, $p < 0.002$), but not in genotype non 3 patients (29% vs 34%, $p = \text{NS}$). Among the SVR, improvement of steatosis was significantly more frequent in genotype 3 patients than in genotype non 3 patients (88% vs 29%; $p = 0.04$). Conversely, among the NR, improvement of steatosis did not differ between genotype 3 and non 3 patients (19% vs 34%; $p = \text{NS}$).

Conclusions: Our results show a significant improvement of steatosis in genotype 3 patients achieving a SVR. They provide further evidence in favor of the direct involvement of HCV in the pathogenesis of hepatic steatosis.

PSYCHOLOGICAL IMPACT OF CHRONIC HEPATITIS C DIAGNOSIS: COMPARISON WITH OTHER STRESSFUL LIFE EVENTS

L. Castera ,^{1,2} A. Constant,³ P.H. Bernard,² V. de Ledinghen,¹ J. Foucher,¹ B. Quintard,³ P. Couzigou,¹

**Presenting Author, ¹Service D'Hepatologie, Hopital Haut Leveque, Pessac, France ²Service D'Hepatologie, Hopital St-Andre, Bordeaux, France ³Laboratoire De Psychologie EA 526, Universite Victor, Segalen-Bordeaux 2, France*

Aim: The psychological issues that patients with HCV face remain poorly known. We prospectively investigated the psychological impact of chronic HCV infection diagnosis.

Methods: 185 consecutive HCV RNA-positive patients (111 men; mean age 45 ± 11 years) were asked to self-grade, using a visual analogue scale (VAS) scoring from 0 to 100 mm: (a) the degree of stress induced by the diagnosis of HCV as compared with 4 other stressful life events (i.e. move, dismissal, divorce, death of a loving person); (b) the self-perceived severity of HCV infection. Anxiety was assessed using the Spielberger State Trait Anxiety Inventory. The influence of sociodemographic parameters such as age, gender, and educational level was also studied.

Results: Diagnosis of HCV was considered as the most stressful event (mean VAS score 72 ± 25) after the death of a loving person (89 ± 13) and a divorce (78 ± 23). It was significantly more stressful than a dismissal (68 ± 30 , $p < 0.04$) and a move (26 ± 24 , $p < 0.0001$). Stress scores were significantly higher in women than in men (79 ± 26 vs 68 ± 22 , respectively; $p < 0.004$). HCV perceived severity was high (74 ± 19) and not related to histological severity (METAVIR fibrosis score). Using multiple linear regression analysis, stress was related to self-perceived severity ($p < 0.0001$) and anxiety ($p < 0.0001$).

Conclusions: Our results, obtained on a large cohort of patients using standardized tools, provide convincing evidence that the psychological and emotional burden perceived by patients with chronic HCV infection is considerable. Appropriate management of the process of imparting a diagnosis of HCV may help to reduce the negative effects of diagnosis.

HEPATITIS C INFECTION IN THE GENERAL URBAN POPULATION: PREVALENCE AND SPECTRUM OF DISEASE

Aim: Prevalence and spectrum of hepatitis C (HCV) infection among adults in Oslo.

Materials and methods: The study was part of the population based Oslo Health Study 2000-2001. It included a random selection of individuals born in 1924, 1925, 1940, 1941, 1955, 1960 or 1970. Sera from 11454 participants were screened for anti-HCV (EIA-3), positive were confirmed (RIBA III) and examined for HCV RNA (PCR). All anti-HCV positive patients were offered clinical evaluation. Routine biochemical liver tests were performed. Candidates for HCV treatment were asked to undergo a percutaneous liver biopsy. The biopsy was assessed with the Knodell histology activity index score.

Results: Among 11454 participants anti-HCV was detected in 78 (0.7%) (95% C.I: 0.6-0.9), HCV RNA in 62 (0.5%) and HCV RNA with raised serum ALT in 46 (0.4%). The peak prevalence of 1.5% was seen among subjects 40 and 45 years old. Being anti-HCV positive was associated with living alone, low education and being unemployed. The prevalence among subjects with an alcohol problem was 4, 4% compared with 0.6% in those without ($p<0.001$) and the prevalence among smokers was 2.0% compared to 0.2% among non-smokers ($p<0.001$). In 33 liver biopsies bridging fibrosis was seen in eight (24%) and cirrhosis in one (3%). The route of transmission was injecting drug use in 67%, transfusion in 6% and unknown in 27%.

Conclusion: In this population-based survey anti-HCV was detected in 0.7%, HCV RNA in 0.5% and HCV RNA with raised serum ALT in 0.4%.

TIME TO DEVELOPMENT OF CHRONIC LIVER DISEASES IN A GENOTYPE 1 DOMINANT POPULATION OF CHRONIC HEPATITIS C VIRUS INFECTION

Aim: Data of 320 hepatitis C pts were retrospectively investigated to define the duration of HCV infection to develop chronic liver disease.

Methods: Total 320 patients (57% female, mean age 49.7); 206 with chronic hepatitis (CH), 67 with cirrhosis, 16 with HCC and 31 ALT normal with CH were included and questioned for transmission routes and time. Anti-HCV was tested by 3rd generation EIA kit. HCV RNA (PCR, Cobas Amplicor, Roche) was positive in 295 pts (95%). HCV genotype detected by Inno Lipa innogenetics kit. Of 103 pts who were tested, 90% was infected by genotype 1 (85 pts 1b), 5 genotype 3a, 3 genotype 2 and 3 genotype 4.

Results: The time between acquiring HCV infection and development of chronic liver disease was 192.4 ± 140.6 (9-600) months for CH, 312.7 ± 147.1 (48-780) for compensated cirrhosis 308.8 ± 145.2 (84-660) for decompensated cirrhosis, 238.4 ± 125.3 (48-480) for HCC and 221.6 ± 133.9 (17-550) for ALT normal CH. Analysis of CH patients revealed different durations of development of CH as 200.0 ± 129.5 (11-504) months in stage 1 and 311.9 ± 145.7 (48-780) in stage 4. The difference in duration of HCV infection between stage 1 and 4 was statistically different ($p<0.001$).

The mean time to develop CH and cirrhosis in this HCV genotype 1b dominant population is 16 years and 26 years respectively. The development of stage 4 CH takes 25 years while this duration for stage 1 disease is 15 years.

Conclusion: The results have confirmed previous knowledge about duration of HCV infection to develop CH and cirrhosis.

RETREATMENT WITH HIGH VS. CONVENTIONAL DOSES OF CONSENSUS INTERFERON AND RIBAVIRIN OF PATIENTS WITH NON-RESPONSE OR RELAPSE AFTER PREVIOUS TREATMENT WITH ALPHA-INTERFERON

W.O. Bocher , P.R. Galle, H.F. Löhrr,

**Presenting Author, ¹ Dept. Internal Medicine, Mainz University, Mainz, Germany*

Background: Retreatment with interferon alpha (IFNa) and ribavirin (riba) leads to viral elimination in less than 15% of patients with non-response to previous therapies. Consensus interferon (CIFN) is a synthetic type I interferon with increased in vitro antiviral activity.

Aim: In this study, it should be assessed whether CIFN might lead to enhanced response rates of patients with chronic hepatitis C.

Methods: 94 patients (age 45 years, male 59%, cirrhosis / bridging fibrosis 64%, genotype-1 71%) with detectable HCV-RNA and elevated ALT after non-response (NR) or relapse (Rel) to IFNa or IFNa/riba were included. They were randomly assigned to treatment arm 1 (CIFN 27mg QD for 2 weeks followed by 18mg QD for 10 weeks, 9mg QD for 12 weeks and 9mg tiw for 24 weeks; ribavirin 800mg QD from weeks 3 - 48) or arm 2 (CIFN 18mg tiw for 12 weeks followed by 9mg tiw for 36 weeks, ribavirin 800 mg QD from the beginning).

Results: In the intention-to-treat-analysis, NR patients treated in arms 1 or 2 exhibited early virological response rates (EVR; week 12) of 58% vs. 39% and end of treatment response rates (ETR; week 48) of 37% vs. 29%, respectively. Even the most-difficult-to-treat subsets of NR patients pretreated with IFN/riba combination or with genotype-1 infection still had ETR rates of 30% vs. 20% or 39% vs. 37% when re-treated in arms 1 or 2, respectively. Rel patients treated in arms 1 and 2 had EVR in 86% and 81%, and ETR in 86% and 58%. Therapy was quite well tolerated and had to be discontinued due to side effects in 10 and 15% of patients treated in arms 1 and 2.

Conclusions: CIFN / riba treatment of patients non-responsive to previous therapies induced promising ETR results. Since the high dose induction regimen appeared superior for most subgroups, viral elimination rates might be further increased by daily dosing of CIFN and weight adjusted ribavirin dosing.

PREDICTIVE VALUE OF EARLY VIROLOGICAL REDUCTION (EVR) IN THE RESPONSE AT 24 WEEKS (W) OF HCV TREATMENT WITH PEG-INTERFERON (PEG-IFN) & RIBAVIRINE (RBV) IN HIV-INFECTED PATIENTS (P)

A.L. Ballesteros , ¹ S. Franco, ¹ D. Fuster, ¹ M.A. Martinez, ¹ L. Acosta, ¹ A. Salas, ¹ C. Rey-Joly, ¹ J. Tor, ¹ R. Planas, ² B. Clotet, ¹ C. Tural, ¹

**Presenting Author, ¹ HIV Unit, Hospital Universitari Germans Trias I Pujol, Badalona, Spain ² Hepatology Unit. Hospital Universitari Germans Trias I Pujol, Badalona, Spain*

Background: In HIV p, early predictors of response to HCV treatment could avoid unnecessary toxicity. Plasma HCV viral load reduction at w12 as a marker of final response in co-infection is under discussion.

Methods: Pilot, prospective trial of directly observed HCV treatment with Peg-IFN (1.5mg/kg/w) & RBV

(10.6mg/kg/day). Quantitative plasma HCV viral load (limit of detection 600 IU/ml) was measured at day1 & w1, 4&12. Qualitative test (limit of detection 50 IU/ml) was performed at the same points if HCV<600 IU/ml. Response at 24w was determined by qualitative assay. We defined 2 criteria of EVR: *1 Quantitative decrease >2log from baseline or negative (-) qualitative test; *2 Negative qualitative test. Sensitivity (S), Specificity (Sp), Negative Predictive Value (NPV) & Positive Predictive Value (PPV) of EVR were calculated.

Results: 28p (18males) were included. 85% had HIV RNA viral load <200cp/ml; mean baseline CD4 554.4/mm³ (225.1). All but 4p were on HAART. HCV Genotypes (gen): (13) 1a/b, (10) 3a, (5) 4c/d [>850000 IU/ml: 8/13, 2/9&2/5 respectively]. 7p (26%) discontinued. On treatment analysis, the global virological response at 24w was 52.4% (11/21): 3a (7/8), 4c/4d (2/5), 1a/b (2/8). Sequential quantitative medians viral load reduction (in log₁₀) are represented on table 1. Sensitivity, NPV & PPV of EVR at the different points are represented on table 2.

Baseline log.	Day1	W1	W4	W12	p-value*
Global (5.4445)	0.4436	0.3087	0.8890	0.6081	0.001
Gen.1&4 (5.5865)	0.2178	-0.1068	0.6433	0.4680	0.064
Gen. 3 (5.1888)	1.1967	1.4485	1.7623	2.6125	0.008

*Wilcoxon test comparing HCV viral load at baseline & W12

*S./Sp/NPV/PPV (%) Day1

Global *1*2	18.2/100/52.6/100	9.1/100/50/100
W1	9.1/100/50/100	9.1/100/50/100
W4	72.7/100/76.9/100	54.5/100/66.7/100
W12	90.9/80/88.9/83.3	81.8/100/83.3/100

*1 Quantitative decrease >2log from baseline or negative (-) qualitative test. *2 (-) Qualitative test

Conclusions: In contrast to genotype 3, a lack of virological response is observed in most genotypes 1&4. A good prediction of the response at w24 was obtained at w12; furthermore, a (-) qualitative test at w12 may discriminate future relapsers.

LONG TERM FOLLOW-UP OF GLYCYRRHIZIN THERAPY IN PATIENTS WITH CHRONIC HEPATITIS C AND NON-RESPONSE TO INTERFERON: META-ANALYSIS OF INDIVIDUAL PATIENT DATA

B.E. Hansen¹, K. Ikeda², B.J. Veldt², E. Verheij¹, H. Suzuki³, S.W. Schalm¹

*Presenting Author, ¹Department Of Gastroenterology & Hepatology, Erasmus Mc, University Medical Center, Rotterdam, Netherlands ²Department Of Gastroenterology, Toranomon Hospital, Tokyo, Japan ³Yamanashi Medical University, Yamanashi, Japan

Background: Glycyrrhizin (SNMC) is used as a treatment for patients with hepatitis C in all academic units in Japan. However until now the long-term consequences of SNMC therapy have not been well documented. Aims: To determine the percentage of IFN non-responder patients with chronic hepatitis C and subsequent SNMC therapy that progress to HCC in comparison to IFN non-responders without SNMC treatment.

Methods: Data were collected from 12 Japanese university and major general hospitals by well-trained professionals. All consecutive chronic hepatitis C patients who received IFN between 1-1-1990 and 31-12-1995 without a sustained response were included.

Results: The number of patients included in the study is 1093. The median follow-up was 6.1 years (5-95 percentile[2.5;9.0 years]). 461 patients received SNMC therapy. In general, patients treated with SNMC suffered from more severe liver disease than those not treated with SNMC. The 5 year overall HCC occurrence was 1.2%, 4.0%, 14% and 27% for fibrosis stage 1, 2, 3 and cirrhosis, respectively. To eliminate

fibrosis stage as a confounder, we selected all patients with fibrosis stage 3 or higher (n=255) at inclusion. Occurrence of HCC during follow-up was reduced in patients treated with SNMC, compared to those who did not receive SNMC (Relative risk 0.52 (95%CI [0.24;1.13]p=0.10). Data were corrected for age, sex, alcohol use, source of infection, concurrent UDCA treatment and ALT level.

Conclusion: SNMC therapy reduces the risk for development of HCC in chronic hepatitis C patients with fibrosis stage 3 or higher, not responding to IFN therapy.

BIOCHEMICAL AND HISTOLOGICAL HEPATIC DISEASE ACTIVITY IN CRYOGLOBULINEMIC PATIENTS

L. Mele , P. Muratori, S. Loffreda, L. Muratori, F.B. Bianchi, M. Lenzi,

* Presenting Author, Department Of Internal Medicine, Cardioangiology, Hepatology. Policlinico S.Orsola-Malpighi, University Of Bologna, Bologna, Italy

Background: The occurrence of circulating cryoglobulins (CG) and associated vasculitis during HCV related chronic liver disease (CLD) is a well documented argue. The recently described interaction between HVR1-E2 region of HCV and CD81 receptor of lymphocytes has been proposed as a pathogenetic link between HCV and immune system.

Aim: To evaluate clinical and histological activity of cryoglobulinemic patients with and without vasculitis. **Methods:** We studied 167 HCV-CLD patients with circulating cryoglobulins, of whom 44 with cryoglobulinemic vasculitis (CV). 128 (76%) out of 167 underwent to liver biopsy; in the remaining 39 patients a clinical diagnosis of cirrhosis was performed. Histological activity was scored as follows: minimal lesions (1), mild (2), moderate (3), severe (4) activity chronic hepatitis and (5) cirrhosis (both clinical and/or histological). The diagnosis of CV was made according to Meltzer's triad.

Results: As shown in the table symptomatic CG positive patients have lower biochemical and histological disease activity and lower number of cirrhosis than controls.

	CG+CV- 123	CG+CV+ 44	p*
Sex M/F	48/75	10/34	<0.03
Age (yrs)	54 (19-87)	59 (26-85)	0.005
DiseaseDur (mo)	91 (6-636)	93 (10-324)	ns
ALT (<40IU)	71 (9-502)	54 (9-330)	0.001
Histol	3.4±1.3 (1-5)	2.7±1.2 (1-4)	0.002
Cirrhosis	40	6	<0.01 [§]

*=Student T Test §=Chi square Test

Conclusions: Histological and biochemical disease activity in presence of cryoglobulinemic vasculitis is low. It is suggested that CG, when associated to a full blown cryoglobulinemic vasculitis, may have a favorable prognostic significance with respect to the underlying liver disease. How the interaction between host and viral factors can alternatively address the clinical spectrum of disease towards prevalent hepatic or extrahepatic involvement remains an open topic.

TREATMENT OF CHRONIC HEPATITIS B/C COINFECTED PATIENTS WITH CONSENSUS INTERFERON / RIBAVIRIN / LAMIVUDINE TRIPLE THERAPY

S. Kaiser , H.G. Hass, M. Gregor,

* Presenting Author, Dept. Of Medicine, University Hospital Of Tuebingen, Tuebingen, Germany

Background: The risk of complications in chronic hepatitis is considerably increased in HBV/HCV coinfecting patients. However, standard interferon / ribavirin therapy shows reduced response rates compared to mono-infected patients.

Aim and Methods: As recent studies have shown improved response rates using consensus interferon (CIFN) in difficult-to-treat patients with hepatitis C, the efficacy of CIFN daily dosing (9 ug QD) combined with lamivudine (100mg QD) and ribavirin (1.000/1.200mg QD) in HBV/HCV coinfecting patients was evaluated. 21 patients (mean age 51.3 yrs., 81% male, all with elevated ALT and viremia for HBV and HCV, all genotype 1) have been included so far. Treatment started with 12 weeks of lamivudine monotherapy, then CIFN and ribavirin was added for another 60 weeks.

Results: After 36 weeks of triple therapy, a negative HBV PCR was observed in 78% and a negative HCV RNA was observed in 72%. The subset of patients having reached end-of-treatment (n=16) and 24 week follow-up (n=9) show response rates of 69% (ETR) and 56% (SR), for HCV. For HBV, 81% of patients so far reached a viral response at end-of-treatment. Interestingly, two patients with a follow-up of one year showed a complete HBV response with seroconversion to antiHbs. Due to side effects CIFN had to be reduced in 2 patients and ribavirin in 3 patients. No increases in lactate were noted when the nucleoside analogs were given together.

Background: CIFN daily dosing therapy together with lamivudine and ribavirin triple therapy thus shows promising response rates in this pilot study.

HISTOLOGICAL DAMAGE IN LIVER BIOPSY SPECIMENS FROM 492 HIV-HCV CO-INFECTED PATIENTS: A EUROPEAN COLLABORATIVE STUDY

M. Romero, ¹ L. Martin-Carbonero, ² Y. Benhamou, ³ M. Puoti, ⁴ J. Rockstroh, ⁵ A. Arizcorreta, ⁶ J.A. Giron, ⁶ V. Asensi, ⁸ A. Gonzalez, ⁷ M. Vogel, ⁵ V. Soriano, ² J. Garcia-Samaniego, ¹

** Presenting Author, ¹Hepatology Unit, Hospital Carlos III, Madrid, Spain ²Infectious Disease Unit, Hospital Carlos III, Madrid, Spain ³Hopital Pitie-Salpetriere, Paris, France ⁴Spedali Civili, Brescia, Italy ⁵University Hospital, Bonn, Germany ⁶Hospital Puerta Del Mar, Cadiz, Spain ⁷Centros Penitenciarios, Madrid, Spain ⁸Hospital General, Oviedo, Spain*

Background: HCV-related liver damage progresses faster in HIV+ patients than in HIV-negatives. In HCV-mono-infected patients with elevated ALT levels, mild liver fibrosis (F0-F1) is recognized in 75% and stages F2-F4 in 25%. This information is not well known for HIV-positives.

Methods: All participants were invited to fill a case report form in which the main demographics, clinical, laboratory and histological findings from HIV-HCV coinfecting patients with elevated ALT levels were recorded. Liver biopsy was performed prior antiHCV treatment.

Results: 492 patients (78.5% males, 86% IDUs, 25% alcohol intake >80g/dl) were analyzed. Median age was 35 years old. Median estimated duration of HCV infection was 14 years. Median CD4 count was 463 cells/ul. Median ALT elevation was 2 fold. Antiretroviral therapy: 43%, and no drugs 57%. HCV genotype was 1: 57%, 2: 1%, 3: 36% and 4: 6.3%. 69% of patients harboured HCV-RNA > 800000 IU/ml. Liver fibrosis stage was F0: 13.2%, F1: 35%, F2: 18.7%, F3: 21.5%, and F4: 12%. In the multivariate logistic regression analysis 3 factors were predictors of severe liver fibrosis: duration of HCV infection > 15 years, age >20 years at the time of HCV infection, and high alcohol intake. Patients estimated to be infected for more than 15 years had severe liver fibrosis in 46%.

Conclusions: More advanced stages of liver fibrosis are seen in HIV-HCV coinfecting patients than in HCV-mono-infected patients. Overall, up to one third of those with elevated ALT levels show severe liver fibrosis (F3-F4), but increases significantly with duration of HCV infection.

PRESENCE OF MULTIPLE HCV GENOTYPES AND RESPONSE TO INTERFERON THERAPY

N. Bzowej, Y. Phung, L. Brooks, M. Bonacini, A. Wakil, R. Gish,

*Presenting Author, Department Of Liver Transplantation, California Pacific Medical Center, San Francisco, CA, USA

Hypothesis: Presence of multiple genotypes is associated with nonresponse to interferon.

Methods: 4 sustained responders (SR), 4 relapsers (R) and 4 nonresponders (NR) were selected. Baseline, end of treatment and follow up serum samples were analyzed. Primers specific for 6 genotypes & 9 subtypes were used to amplify the core region. Extended PCR (45 cycles) was used. Genotypes were identified by comparison of visible bands on gels with known standards. Negative controls were performed. Results: At baseline, patients with 1 or 2 genotypes by commercial assay were found to have between 2 and 4 genotypes. Results for SR and R are shown below. NR demonstrated persistence of multiple genotypes during therapy and at follow up.

Summary:

1)Multiple genotypes is common; 2)Patients with multiple genotypes at baseline had detectable viremia at follow up; 3)Genotype 1a appeared to be more resistant to therapy; 4)In some, IFN therapy resulted in detection of additional genotypes not observed at baseline.

Conclusions: 1)SR determined by commercial assays may represent sustained suppression of virus rather than clearance. This may explain the development of late relapse; 2)Host responses to virus and presence of multiple HCV genotypes may represent important factors associated with nonresponse. Further study is required to determine if lower viral clearance is attributable to genotype 1a.

Patient Group	Commercial Genotype	Baseline Genotype (30 cycles PCR)	Baseline Genotype (45 cycles PCR)	End of Treatment Genotype (45 cycles PCR)	Follow Up Genotype (45 cycles PCR)
SR 1	2	1a, 2a	1a, 2a	1a	1a
SR 2	1a	1a	1a, 1b, 2a, 3a	1a	NA
SR 3	1a	PCR negative	1a, 2a, 2b, 3a	1a	1a
SR 4	NA	3a	1a, 2a, 3a	1a	1a
R 1	1a	1a, 2a	1a, 2a, 2b	1a	1a, 2a
R 2	1a	1a	1a, 3b	1a	1a, 2a, 2b, 3b
R 3	1a	1a, 1b, 2a	1a, 2a, 2b	1a	1a, 2b
R 4	1a, 1b	1a, 1b, 2a	1a, 1b, 2a	1a	1a, 2a, 2b

* NA = not available

IMPACT ON LIVER HISTOLOGY AND RELATIONSHIP WITH RESPONSE TO COMBINATION THERAPY OF OCCULT HEPATITIS B VIRUS INFECTION IN PATIENTS WITH CHRONIC HEPATITIS C

P. Fabris,¹ D. Brown,² G. Tositti,¹ L. Bozzola,³ M. T. Giordani,¹ P. Bevilacqua,³ F. de Lalla,¹ G. Dusheiko,²

*Presenting Author, ¹Department Of Infectious Diseases, S. Bortolo Hospital, Vicenza, Italy ²Centre For Gastroenterology And Hepatology, Royal Free Hospital, London, UK ³Department Of Pathology, S. Bortolo Hospital, Vicenza, Italy

Aims: To evaluate the prevalence of occult HBV infection and assess its impact on liver biochemistry, HCV viral titre, liver histology and on outcome of therapy in patients with chronic hepatitis C.

Methods: Liver biopsies and serum samples were collected from 51 patients (84% IVDUs) with HBsAg negative chronic hepatitis C, and tested for HBV-DNA with nested PCR. Liver biopsies were further studied

histologically, with morphometric analyses and immunostaining techniques. Twenty-five were treated with alpha Interferon plus ribavirin and followed for at least 18 months.

Results: HBV DNA was detected in 29.4% of liver tissue specimens and in only one (1.9%) serum sample. Three liver specimens were positive for Surface gene, 9 for Core gene, 3 for both and none for the X gene. No significant difference in mean transaminase values, HCV viral titre, HCV genotype, or grading and staging and morphometric analysis was observed in patients with or without HBV DNA. Moreover, all 51 liver specimens were negative for both HBsAg and HBeAg. Sustained response to combination therapy was achieved in 40% of patients with and in 53% of patients without HBV DNA in the liver specimens (P=NS).

Conclusions: HBV DNA is frequently found in the liver of patients with chronic hepatitis C. However, the lack of any significant impact on HCV viral titre, liver enzymes, histological parameters and response to therapy, suggests that in most cases HBV DNA detected in the liver by PCR may be either an integrated or low level replicative form

PATHOLOGICAL EVOLUTION OF HCV-HEALTHY CARRIERS: A MULTIVARIATE ANALYSIS

R. Sobesky, P. Lebray, B. Nalpas, A. Vallet-Pichard, H. Fontaine, J.L. Lagneau, S. Pol,

* *Presenting Author, Service D'Hepatology And INSERM U370, Paris, France*

Aim: To determine factors associated with fibrosis progression in HCV-infected patients without significant initial pathological lesions.

Methods: 76 (34M/42F) HCV-infected patients with normal liver (Knodell score ≤ 3) with 2 biopsies, detectable HCV-RNA and no treated were included. We assessed factors of progression including ALT, date and age at contamination, infection duration, viral genotype and load, BMI and alcohol consumption.

Results: Mean age at contamination and at the first biopsy was 25 and 38 years respectively. Median duration of infection and time between paired biopsies was 13 and 4 years respectively. ALT was normal in 43.4%. 50% had progression of the hepatitis activity index (HAI) and 34% of fibrosis. The median difference of HAI and fibrosis score between biopsies was low; 1.5 and 0.0, respectively. By univariate analysis, there was no difference between HAI or fibrosis evolution with genotype or viral load. A higher fibrosis progression ($p=0.03$) was observed in patients with BMI >25 . Fibrosis progression was correlated interval between biopsies ($p=0.01$). A significant progression of activity (1.7 vs 0.4 $p < 0.05$) or fibrosis (0.9 vs 0.0 $p < 0.01$) was observed in patients with elevated ALT. There was a significant correlation between activity progression and fibrosis progression ($p=0.003$). After multivariate analysis, fibrosis progression was associated with elevated ALT, BMI >25 and the interval between 2 biopsies.

Conclusion: In patients without significant initial histological lesion, there is no fibrosis progression in 66% of patients. Fibrosis progression is associated with elevated ALT, BMI >25 .

Pharmacokinetics of Pegasys Compared to PEG-Intron in Treatment-Naïve Patients with Chronic Hepatitis C

Abstract Summary

The currently available pegylated interferon (PEG-IFN) formulations, PEG-IFN alfa-2a (40KD, PEGASYS) and PEG-IFN alfa-2b (12KD, PEG-Intron), have different pharmacokinetic profiles.

Aim: This current study, conducted at the University of Pavia, Italy, was to compare the pharmacokinetics of

the two PEG-IFNs in patients with chronic hepatitis C (CHC). 30 treatment naive patients with CHC and persistently elevated ALT levels have been randomized to receive 180 mcg PEGASYS once-weekly (n=16) or 1.0 mcg/kg once-weekly of PEG-Intron (n=14). Serum concentrations of both PEG-IFNs were measured at baseline and 24, 48, 120 and 168 hours after administration using a quantitative sandwich ELISA (lower limit of detection 125 pg/ml).

Serum concentration of PEG-Intron achieved maximum levels at 24 hours after injection and decreased rapidly until 120 hours. Drug was undetectable 120 and 168 hours after injection in 7 (50%) and 11 (78%) subjects, respectively. In contrast, PEGASYS concentrations increased continuously overtime, reaching maximum levels from 48 to 168 hours.

Conclusions: The investigators conclude, "Our data demonstrate substantial differences in plasma concentration profiles between PEGASYS and PEG-Intron. Five days after injection concentrations of PEG-Intron are marginal or undetectable, while those of PEGASYS remain stable overtime.

"These findings suggest that PEG-Intron administration should be intensified to twice weekly to avoid "blips" in viral replication. Differences in pharmacokinetics could explain the differences observed in HCV decay."
3/24/03

Reference

R Bruno and others. PHARMACOKINETICS OF PEGINTERFERON ALFA-2A (40KD, PEGASYS) COMPARED TO PEGINTERFERON ALFA-2B (12KD, PEGINTRON) IN NAIVE PATIENTS WITH CHRONIC HEPATITIS C (CHC). Abstract 4203.00. *Abstracts of the 38th Annual Meeting of the European Association of the Study of the Liver (EASL)*.

Pegasys (pegylated interferon alfa-2a) or Roferon A (standard interferon alfa-2a) Plus Ribavirin Plus Amantadine in HCV Treatment-Naïve Patients

Abstract Summary

A recent individual meta-analysis on 972 patients from 6 European Centers demonstrated that the addition of amantadine (AMA) to standard IFN-alfa-2a (Roferon A) significantly increases the efficacy of IFN monotherapy.

In this large randomized, controlled trial, Italian researchers investigated whether triple therapy of AMA plus ribavirin (RBV) and pegylated IFN-alfa-2a (Pegasys) or standard IFN-alfa-2a improves the success rate over dual therapy with standard IFN/RBV.

Overall, 360 naïve patients with biopsy-proven chronic hepatitis C (CHC), elevated ALT and positive HCV-RNA were randomised to Pegasys 180mcg once-weekly plus RBV 1000-1200mg/daily plus AMA 200mg/daily (group A) or Roferon A 3MIU thrice-weekly plus RBV 1000-1200mg/daily plus AMA 200mg/daily (group B) or Rofereon A 3MIU thrice-weekly plus RBV 1000-1200mg/daily (group C) for 48 weeks with a 24-week follow-up.

Of the 360 patients enrolled, 55.5% were male; mean age 51 years (range 20-65), mean weight 71.6 Kg. Genotype 1b was detected in 48%, 61%, and 54% of patients in group A, B, and C, respectively. Less than 10% of patients in each group were cirrhotics.

Treatments were well tolerated with a dropout rate of 11%, 11% and 13%, respectively. Virological and biochemical responses are reported in the table.

Conclusions: In naïve patients, Pegasys +RBV+AMA induces End-Of-Treatment-Response (EOTR) higher when compared to dual or triple therapy with standard IFN.

Note: Sustained viral response (SVR) data will not be available until the recently-cancelled 38th annual EASL meeting takes place. 03/21/03

Reference

A Mangia and others. A RANDOMISED CONTROLLED TRIAL ON PEGYLATED INTERFERON ALFA-2A (40KD) (PEGASYS) OR IFN ALFA-2A (ROFERON-A) PLUS RIBAVIRIN (RBV) AND AMANTADINE (AMA) VS IFN ALFA-2A AND RBV IN NAÏVE PATIENTS WITH CHRONIC HCV. Abstract 4184.00. *Abstracts of the 38th Annual Meeting of the European Association of the Study of the Liver (EASL)*.

Patients with High HCV Viral Load, Genotype 1 and Cirrhosis May Require More Than 48 Weeks Combination Therapy with Pegasys + Copegus

Abstract Summary

Some patients treated for chronic hepatitis C (CHC) still relapse after an end-of-treatment (EOT) virologic response (VR), particularly patients infected with HCV genotype 1.

The present study was a multicenter trial to determine the frequency of relapse in patients treated with Pegasys (peginterferon alfa -2a) plus Copegus (ribavirin) and to identify baseline parameters associated with viral relapse.

1375 CHC patients received Pegasys 180 mcg/week plus ribavirin 800-1200 mg/day for 24 or 48 weeks. Sustained VR was defined as undetectable HCV RNA at the end of follow-up; and relapse, as detectable HCV RNA following a documented EOT response.

At follow up, high baseline viral load, and, to a lesser degree, cirrhosis, were found to be associated with relapse, particularly in HCV genotype 1 patients.

Conclusions:

- ◆ Treatment with Pegasys/ribavirin results in lower relapse rates than monotherapy in all patients;
- ◆ CHC genotypes 2/3 patients experience lower relapse, regardless of ribavirin dose given, compared with HCV genotype 1 patients whose relapse is dependent on ribavirin dose and duration of treatment.
- ◆ More than 48 weeks treatment for CHC patients with high baseline viral loads, HCV genotype 1, and cirrhosis may be necessary and should be investigated. 3/21/03

Reference

V Balan and others. PREDICTORS OF VIROLOGIC RELAPSE IN PATIENTS WITH CHRONIC HEPATITIS C (CHC) TREATED WITH PEGINTERFERON ALFA -2A (40KD) (PEGASYS) ALONE OR IN COMBINATION WITH RIBAVIRIN (COPEGUS). Abstract 3671.00. *Abstracts of the 38th Annual Meeting of the European Association of the Study of the Liver (EASL)*.

Pegasys + Copegus Is Cost-effective Compared with Rebetron in Treatment-Naïve Patients, Regardless of HCV Genotype

Abstract Summary

In adults with previously untreated chronic hepatitis C (CHC) Pegasys (peginterferon alfa -2a) + Copegus

(ribavirin) + (PEG) obtains a higher rate of sustained virological response (SVR) than non-pegylated combination therapy (non-PEG), but it is still unproven whether this increase is cost-effective.

The researchers of the present study constructed a Markov model of disease progression in which cohorts of hepatitis C virus (HCV) genotype 1 and non-1 patients received PEG or non-PEG for 48 and 24 weeks, respectively, and were followed for their expected lifetime.

The reference patient was a 45-year-old male with CHC without cirrhosis. The SVRs to PEG and non-PEG were 46% and 36% for HCV genotype 1 and 76% and 61% for non-1, respectively. Quality of life and costs for each health state were based on literature and on Italian treatment patterns. Costs in 2002 Euros € and benefits were discounted at 3%.

In HCV genotype 1, PEG increases life expectancy (LY) by 0.78 years and quality-adjusted life expectancy (QALY) by 0.67 years compared to non-PEG. The incremental cost per QALY gained is € 12, 026.

In HCV non-1 genotype patients, PEG increases LY by 1.17 and QALY by 1.01 years in comparison to non-PEG. The incremental cost per QALY gained is € 4, 289. Using population-based HCV genotype distribution estimates, the weighted average incremental cost-effectiveness ratio for all genotypes was € 9, 473 per QALY.

Conclusion: Pegasys + Copegus is cost-effective compared with standard interferon alfa-2b/ribavirin (Rebetron) for treatment of naive adults with CHC, regardless of HCV genotype. 3/21/03

Reference

SD Sullivan and others. A COMPARISON OF COST-EFFECTIVENESS OF PEGINTERFERON ALFA-2A (40KD) (PEGASYS) PLUS RIBAVIRIN (COPEGUS) VS INTERFERON ALFA-2B PLUS RIBAVIRIN AS FIRST TREATMENT OF CHRONIC HEPATITIS C (CHC). Abstract 3722.00. *Abstracts of the 38th Annual Meeting of the European Association of the Study of the Liver (EASL)*.

Therapy with Pegasys + Ribavirin + Amantadine Shows Significantly Better 6-month Virological Response Than Treatment with Roferon + Ribavirin + Amantadine in Non Responders Previously Treated with Roferon + Ribavirin

Abstract Summary

Despite the use of combination therapy with Roferon/Ribavirin (IFN+RBN), a large proportion of HCV positive patients does not respond to therapy. The current study is evaluating the benefit of a triple combination regimen (PEG-IFN or daily IFN+RBV+AMA) for patients previously non responder to IFN/RBV.

228 patients who failed to respond to a prior course of at least 12-week of IFN/RBV therapy, have been randomized to receive 180 mcg once-weekly of PEG-IFN alfa-2a (40KD) + RBV (800-1000mg/day) + AMA (200mg daily) (group A) or IFN alfa-2a (6 MIU daily for 4 weeks, 3 MIU daily for 20 weeks, and then 3 MIU thrice weekly for 24 weeks) +RBV (800-1000mg/day) +AMA (200mg/day) (group B) for 48 weeks with a 24-week follow-up.

Patients with detectable HCV-RNA after 24 weeks of treatment were considered non responders, and therapy discontinued.

Of 228 patients enrolled, 137 have completed at least 24 weeks of therapy. Patients baseline characteristics did not differ in group A vs group B.

No severe or unexpected side effects were observed in either group, 17% of patients discontinued therapy. Dose reduction due to PEG-IFN was 19%, to daily IFN 8% and to RBV 19%. Virological response at 24-

week therapy was 53% and 33% (P=0.02) in patients treated with PEG-IFN and daily IFN respectively. This difference was more evident in patients with genotype 1 (55% vs 31%, P=0.01).

Conclusions: A proportion of non responders to IFN/RBV shows a virological response at 24 week triple therapy. A significantly better 6-month virological response is observed in patients treated with PEG-IFN.
03/21/03

Reference

S. Fargion and others. PEGINTERFERON ALFA-2A (40KD) (PEGASYS) PLUS RIBAVIRIN (RBV) AND AMANTADINE (AMA) VS INDUCTION THERAPY WITH INTERFERON ALFA-2A (ROFERON-A) PLUS RBV AND AMA IN IFN/RBV NONRESPONDER PATIENTS WITH CHRONIC HEPATITIS C (CHC). Abstract 3794.00. *Abstracts of the 38th Annual Meeting of the European Association of the Study of the Liver (EASL).*

Pegasys (peginterferon alfa-2a) Plus Amantadine May Be Effective Alternative Regimen for Patients Intolerant to Ribavirin

Abstract Summary

Pegylated interferon (PEG-IFN) plus ribavirin (RBV) is currently the standard of care for most patients with chronic hepatitis (CHC). The usefulness of amantadine (AMA) as an adjunct to PEG-IFN in treating naïve patients with CHC is still controversial.

Underway at 49 multiple medical centers in Italy, the present randomized trial compares the efficacy and tolerability of combination regimens of Pegasys with RBV or AMA. A total of 734 HCV-RNA positive naïve patients with raised ALT and biopsy-proven CHC have been randomized to 180mcg once weekly of Pegasys with RBV (1-1.2g/daily) or AMA (200mg/daily) for 48 weeks with a 24-week follow-up.

Demographic data of the 734 patients enrolled to date: M/F ratio 2: 1, mean age 45.2 years, mean weight 72.9 kg, mean ALT 131.3 IU/L. 28% of them were cirrhotics, and 58% were infected by HCV genotype 1 or 4. Their mean baseline HCV-RNA was 650 log₁₀ IU/mL.

No severe or unexpected side effects were observed in either group. 6.3% (n=47) have discontinued treatment for different reasons. The virological response is reported in the table below. At the time of the meeting sustained viral response (SVR) will be available for over 150 patients.

Conclusions: As expected, a more favorable efficacy trend was observed in the Pegasys + RBV arm with respect to Pegasys + AMA arm. This trend was more evident in the difficult-to-treat patients (genotype 1, 4). If these primary virological response rates will translate into corresponding SVR rates, an effective alternative combination regimen will be in place for those patients who can't tolerate RBV or is contraindicated. 3/21/03

Reference

G Ideo and others. PEG-IFN ALFA-2A (40KD) (PEGASYS) PLUS AMANTADINE (AMA) OR RIBAVIRIN (RBV) IN NAÏVE PATIENTS WITH CHRONIC HEPATITIS C (CHC). Abstract 3870.00. *Abstracts of the 38th Annual Meeting of the European Association of the Study of the Liver (EASL).*

After 24 Weeks of Pegasys/Ribavirin Combination Treatment, Pegasys Monotherapy for 22 Weeks Results in Higher Rate of Virological Breakthrough Than Continued Combination Therapy

Abstract Summary

Recent clinical studies have shown that patients infected with HCV genotype 1 derive significant benefit from combination therapy with peginterferon plus ribavirin (RBV) given for 48 weeks. However, ribavirin may have severe side effects that may lead to discontinuation of the drug.

The objective of this study was to determine if shorter RBV administration could improve tolerance without altering efficacy in patients infected with HCV genotype 1 who respond to combination therapy.

524 naive patients with HCV genotype 1 chronic infection were included. They received Pegasys (peginterferon alfa 2-a) 180mcg/week plus RBV (800mg/day) for 24 weeks. The virologic responders at week 24 were randomized at week 26 into: Group A Pegasys plus ribavirin, or group B, Pegasys alone for 22 additional weeks. Qualitative HCV-RNA detection was performed at weeks 30, 36, 42, 48, 52, 60, and 72 in each group.

Results of preliminary analysis: At week 24, 366 patients were negative by PCR, which corresponds to a virologic response rate of 70%. Only age (<44vs>44 years), fibrosis (F1-2 vs F3-4) and male gender were independently predictive of response at week 24. At week 26, 360 patients were randomized. Currently, 234 patients have reached to week 48 and were tested for HCV RNA: 2.7% patients (3/ 111) relapsed during therapy in group A vs 11.4% (14/123) in group B.

Conclusions: The results of this preliminary analysis reveal a trend toward a higher rate of virological breakthrough in the peginterferon alfa-2a monotherapy arm after week 24. 3/19/03

Reference

JP Bronowicki and others. EFFICACY OF PEGINTERFERON ALFA-2A (40KD) (PEGASYS) PLUS RIBAVIRIN FOR 24 WEEKS IN GENOTYPE 1 PATIENTS WITH CHRONIC HEPATITIS C FOLLOWED BY MONO OR COMBINATION THERAPY FOR 22 WEEKS: PRELIMINARY ANALYSIS OF AN OPEN, MULTICENTER, RANDOMIZED TRIAL. Abstract 3919.00. *Abstracts of the 38th Annual Meeting of the European Association of the Study of the Liver (EASL).*

CYTOKINE LEVELS IN PERIPHERAL BLOOD OF CHRONIC HEPATITIS C (CHC) PATIENTS PRE- AND POST-TREATMENT WITH PEG-INTERFERON ALFA-2B AND RIBAVIRIN

K. Kaligeros*, V. Arseniou, L. Tsakalia, M. Demonakou, M. Lagoudakis, M. Agioutantis,

*Presenting Author, ¹1st Pathology Clinic, 1st IKA Hospital, Melissia, Greece ²Gastroenterology Clinic, 1st IKA Hospital, Melissia, Greece ³Center for Viral Hepatitis Control, 1st IKA Hospital, Melissia, Greece ⁴Histology Lab, Sismanoglion Hospital, Melissia, Greece

AIMS: To evaluate the role of TH1 (IL-2, IFN-gamma and TNF-alfa) and TH2 (IL-4 and IL-10) cytokines during HCV infection. **METHODS:** 50 CHC patients received: Arm A: interferon alfa-2b (IFN-a2b) 3 MIU TIW (n=10), Arm B: IFN-a2b 3 MIU TIW + ribavirin 800-1200 mg QD (n=15), Arm C: peg-IFN-a2b 1.5 mcg/kg + ribavirin 800-1200 mg QD (n=25). All patients were monitored by biopsy, HCV-RNA, genotype; cytokine levels were measured pre-treatment and at week 24.

RESULTS: Levels of IL-2, TNF-alfa, IFN-gamma, IL-4 and IL-10 were independent from HCV viral load and genotype, ALT levels, patient age, gender and hepatic histology. IL-2 levels did not show significant differences pre and during treatment. IL-4 and IL-10 levels were high pre-treatment and exhibited significant and progressive declines during treatment. Specifically, pre-treatment IL-10 levels were on average 1000-1100 pg/ml, and dropped to 500 pg/ml for Arm A, 400 pg/ml for Arm B, and 300 pg/ml for Arm C. For IL-4,

pre-treatment levels were 700 pg/ml and week 24 levels dropped to 350 and 300 pg/ml for Arms A & B respectively; Arm C patients had pretreatment IL-4 levels of 850 pg/ml which dropped to 230 pg/ml by week 24.

CONCLUSIONS: Our preliminary data show that peg-IFN-a2b drastically reduces the levels of IL-4 and IL-10, likely due to its steady pharmacokinetics, resulting in an increase of Th1 activity and antiviral activity. Further analyses are required to establish cytokine patterns during treatment of CHC patients.

THE INFLUENCE OF ANALYTIC TIME HORIZON AND TREATMENT MANAGEMENT ALGORITHMS ON THE COST OF PEGINTERFERON ALFA-2B PLUS RIBAVIRIN THERAPY FOR CHRONIC HEPATITIS C

U. Siebert*, ^{1,2}G. Sroczynski, ¹J. Wasem, ³P. Aidelsburger, ³S. Rossol, ⁴J.B. Wong, ⁵ German Hepatitis C Model (GEHMO) Group,

*Presenting Author. ¹Harvard School Of Public Health, Boston, USA ²University Of Munich, Munich, Germany ³University Of Greifswald, Greifswald, Germany ⁴University Hospital Mannheim, Mannheim, Germany ⁵Tufts University School Of Medicine, Boston, USA

Introduction: Cost estimates for antiviral therapy for chronic hepatitis C (CHC) often neglect dose reductions/discontinuations, clinical management algorithms, and future savings associated with the prevention of advanced liver disease. Objective: To assess the antiviral treatment (AVT) costs associated with peginterferon alfa-2b plus ribavirin in Germany. Methods: Clinical and drug utilisation data were derived from a clinical trial (Manns, Lancet). Analysed treatment options were no antiviral therapy (NoAVT), peginterferon alfa-2b plus fixed dosage of ribavirin (Peg-fR), and peginterferon alfa-2b plus weight-based dosage of ribavirin (Peg-wbR). Examined scenarios were 1) full dosing AVT for 48 weeks (Full-AVT); 2) stoppage of AVT in HCV-positive patients after 24 weeks (Stop-AVT); 3) consideration of AVT stoppage algorithm plus actual dose reductions/ discontinuations (Actual-AVT); 4) net lifetime costs after subtracting future savings due to prevented advanced liver disease (Life). A validated Markov model (German Hepatitis C Model) was used to project future costs of CHC.

Results: The table shows AVT and lifetime costs for each strategy. Consideration of stoppage algorithm and actual drug utilisation lead to substantial reductions in expected AVT costs. In the lifetime analysis, AVT costs were offset by savings from preventing future disease by more than 85%, and incremental costs for AVT were less than 2, 100 €. After applying a 3% annual discount rate as recommended for pharmacoeconomic studies (Life-D), future savings still offset AVT costs by 47%.

Conclusion: Health policy decision making for CHC should consider actual expected AVT costs based on routine clinical management algorithms and a time horizon beyond the first year.

Costs (in EUR)	Full-AVT	Stop-AVT	Actual-AVT	Life	Life-D
NoAVT	---	---	---	25,500	14,100
Peg-fR	21,600	17,800	14,500	27,600	21,800
Peg-wbR	23,700	21,800	15,900	27,400	22,400

CHRONIC HEPATITIS C (CH-C) GENOTYPE 1: AN INDEPENDENT, MULTICENTER RCT COMPARING PEG-IFN ALFA-2B 12KD PLUS RIBAVIRIN (RBV) AND IFN ALFA-2B PLUS (RBV) IN NAIVE PATIENTS

S. Bruno, ³C. Camma*, ^{1,2}V. Di Marco, ¹M.G. Rumi, ⁴M. Vinci, ⁵M. Camozzi, ⁵D. Di Bona, ¹M. Mondelli, ⁶M. Colombo, ⁴A.

*Presenting Author. ¹Cattedra Di Gastroenterologia, Istituto Di Clinica Medica, University Of Palermo, Palermo, Italy ²IBIM, Consiglio Nazionale Delle Ricerche, Palermo, Italy ³Istituto Di Scienze Biomediche, San Paolo University Of Milano, Milano, Italy ⁴Cattedra E Unita' Operativa Di Gastroenterologia, IRCCS Ospedale Maggiore, University Of Milano, Milano, Italy ⁵Epto-Gastroenterologia, AO Niguarda, Milano, Italy ⁶Dipartimento Di Malattie Infettive, IRCCS, Policlinico S. Matteo, University Of Pavia, Pavia, Italy

Background: In patients with CH-C infected with genotype-1 the efficacy of treatment is far from satisfactory. Aims. To assess in a multicenter RCT on patients with CH-C genotype 1 the safety and efficacy of high dose of RBV in combination with PEG-IFN ALFA-2b 12 KD or high dose of standard IFN ALFA-2b.

Methods: 313 consecutive naïve patients were randomly assigned to receive IFN ALFA-2b (6MU subcutaneously on alternate days) for 48 weeks (IFN, n=150) or PEG-IFN 12 KD 100 microg q.w. for 8 weeks then 50 microg q.w. for 40 weeks (PEGIFN, n=163). RBV 1000 mg (BW < 75 kg) or 1200 mg/day was given for the entire period. Subjects with detectable HCV-RNA by AMPLICOR at week 24 stopped treatment. Virological response at the end of treatment (ETR) and 24 weeks after the cessation of treatment (SVR), were analysed and reported as intention-to-treat. Results. Treatment withdrawal for side effects was significantly more frequent in IFN group than in PEGIFN group (32% vs 20% respectively, p=0.014). ETR was observed in 61/150 patients (40.6%) in IFN group and in 88/163 (53.9%) in PEGIFN group (p=0.018). SVR was observed in 44/150 patients (29.3%) in IFN group and in 66/163 (41.1%) in PEGIFN group (p=0.030).

Conclusions: In naïve subjects with CH-C genotype-1 PEG-IFN 12 KD at a dose of 100 microg q.w. for 8 weeks then 50 microg q.w. for 40 weeks in combination with RBV is significantly more effective and better tolerated than high dose of standard IFN ALFA-2b plus RBV.

EVALUATING RAPID VIROLOGICAL RESPONSE REDUCES RIBAVIRIN AND PEGINTERFERON ALFA-2B TREATMENT COSTS FOR CHRONIC HEPATITIS C IN THE UNITED KINGDOM

J. B. Wong*, ¹ W.M. Rosenberg, ² M.P. Manns, ³ G.L. Davis, ⁴ J.G. McHutchison, ⁵ J.K. Albrecht, ⁶ I.H.I.T. Group, ⁶

*Presenting Author, ¹Tufts-New England Medical Center, Boston, MA, USA ²University Of South Hampton, South Hampton, UK ³Medizinische Hochschule Hannover, Hannover, Germany ⁴Baylor University Medical Center, Dallas, TX, USA ⁵Duke Clinical Research Institute, Duke University Medical Center, Raleigh, NC, USA ⁶Schering-Plough Research Institute, Kenilworth, NJ, USA

Introduction: Monitoring 12-week antiviral treatment response for chronic hepatitis C has been recommended to reduce treatment morbidity and expense. Aim: To estimate antiviral drug costs using alternative management algorithms. Methods: We analyzed actual drug dosing for 511 patients intended to receive 800 mg of ribavirin daily and 1.5 µg/kg peginterferon a-2b weekly (PegR8) for 48 weeks and for the subset receiving >10.6 mg/kg of ribavirin (PegRW) (Manns Lancet 2001). Based on doses used and UK vial sizes and costs, we determined the drug costs for 1) full dosing (Full), 2) intent to treat with reductions and discontinuations as occurred in the trial (ITT), 3) discontinuing therapy in those who were HCV RNA-positive after 24 weeks (Stop24), 4) criteria in Stop24 and also limiting therapy in those with genotype 2/3 to 24 weeks (Stop2/3), and 5) criteria in Stop2/3 and also discontinuing therapy in those viral positive with <2 log drop in viral load in non-genotype 2/3 patients after 12 weeks (Stop12).

Results: For both regimens, management algorithms monitoring rapid virological response during treatment would have resulted in substantial reductions in antiviral drug costs. PegR8 had the following costs: £11, 935 for Full, £9, 801 for ITT, £8, 549 for Stop24, £7, 226 for Stop2/3, and £6, 718 for Stop12 (44% reduction vs Full). RegRW had the following costs: £13, 033 for Full, £10, 754 for ITT, £9, 476 for Stop24, £7, 954 for Stop2/3, and £7, 442 for Stop12 (43% reduction vs Full). Similar cost reductions were also found for genotype 1 and 2/3 subgroups.

Conclusion: Our results suggest that evaluating rapid virological response substantially reduces antiviral drug costs. Individual decisions to continue antiviral treatment should also consider the variability in the accuracy of quantitative viral assays, patient preferences, and the pending results of ongoing studies of treatment maintenance in those with advanced fibrosis.

IS PEGINTERFERON ALFA-2B PLUS RIBAVIRIN COST-EFFECTIVE FOR TREATING CHRONIC HEPATITIS C IN THE UNITED KINGDOM?

J.B. Wong*, ¹ W.M. Rosenberg, ² M.P. Manns, ³ J.G. McHutchison, ⁴ G.L. Davis, ⁵ J.K. Albrecht, ⁶ I.H.I.T. Group, ⁶

*Presenting Author, ¹Tufts-New England Medical Center, Boston, MA, USA ²University Of South Hampton, South Hampton, UK ³Medizinische Hochschule Hannover, Hannover, Germany ⁴Baylor University Medical Center, Dallas, TX, USA ⁵Duke Clinical Research Institute, Duke University Medical Center, Raleigh, NC, USA ⁶Schering-Plough Research Institute, Kenilworth, NJ, USA

Introduction: Recently developed treatment algorithms can lead to antiviral stoppage after 12 weeks because of persistent PCR positivity with <2 log decrease in viral load, thereby reducing drug morbidity and costs in those unlikely to benefit from further therapy. Aim: To examine the cost-effectiveness of peginterferon a-2b+ribavirin using optimized treatment algorithms.

Methods: Using data from Manns Lancet 2001, we compared 1) no antiviral therapy (NoRx), 2) interferon a-2b+ribavirin (IR), 3) peginterferon a-2b+800 mg ribavirin (PegR8) and 4) peginterferon a-2b+>10.6 mg/kg ribavirin (PegRW). Lifelong clinical and economic outcomes were based on computer cohort simulation (Wong JAMA 1998). Drug costs were based on doses used and UK vial sizes and costs. Cost-effectiveness results are presented as incremental cost per discounted (3%) quality-adjusted life year gained.

Results: Antiviral treatment reduced the future cost of hepatitis C complications by £5,700 to £7,400. Compared to NoRx, cost-effectiveness ratios were £920 for IR, £2100 for PegR and £1900 for PegRW. Compared to IR, cost-effectiveness ratios were £9100 for PegR and £5200 for PegRW. The cost-effectiveness of PegRW vs PR was £960. For genotype 1, cost-effectiveness ratios were £2300 for IR, £3500 for PegR and £3100 for PegRW (all vs NoRx). Compared to IR, cost-effectiveness ratios were £7600 for PegR and £4700 for PegRW. The cost-effectiveness of PegRW vs PegR was £580. For genotype 2/3, IR was cost-saving, and cost-effectiveness ratios were £450 for PegR and £440 for PegRW (all vs NoRx). Compared to IR, cost-effectiveness ratios were £24,700 for PegR and £7300 for PegRW. The cost-effectiveness of PegRW vs PegR was £340. Conclusion: Weight-based peginterferon a-2b+ribavirin should be cost-effective.

EFFICACY OF PEGYLATED INTERFERON ALPHA-2B IN COMBINATION WITH RIBAVIRIN IN PATIENTS WITH CHRONIC HEPATITIS C NON-RESPONDERS TO A PREVIOUS TREATMENT

M. Chousterman*, ¹ V. Auray-Cartier, ¹ H. Hagege, ¹ J.P. Arpurt, ² P. Cassan, ³ J. Denis, ⁴ D. Gargot, ⁵ B. Nalet, ⁶ O. Nouel, ⁷ A. Pariente, ⁸

C. Wartelle-Bladou, ⁹ Angh-Ribapeg Non-Responders Study Group, ¹⁰

*Presenting Author, ¹CHI De Creteil, Creteil, France ²CH D'Avignon, Avignon, France ³CH De Vichy, Vichy, France ⁴CH De Corbeil, Corbeil, France ⁵CH De Blois, Blois, France ⁶CH De Montelimar, Montelimar, France ⁷CH De Saint Briec, Saint Briec, France ⁸CH De Pau, Pau, France ⁹CH D'Aix En Provence, Aix En Provence, France ¹⁰CH De Montfermeil, Montfermeil, France

The efficacy of pegylated interferon alfa-2b plus ribavirin in patients resistant to interferon monotherapy or

standard combination therapy is unknown.

Aim: To compare the efficacy and safety of two dose regimens of pegylated interferon alfa-2b (PEG-IFN) plus ribavirin (RBV) in non-responders to interferon monotherapy or standard combination therapy.

Methods: 233 patients with chronic hepatitis C have been randomized to receive: group 1: PEG-IFN 2.0 µg/kg/wk + RBV 800 mg daily x 8 weeks, then PEG-IFN 1.0 µg/kg/wk plus RBV 800 mg daily x 40 weeks, or group 2: PEG-IFN 1.0 µg/kg/wk plus RBV 800 mg daily x 48 weeks. Results: Baseline characteristics included: genotype 1: 69%, HCV RNA titer > 800000 IU/ml: 66%, cirrhosis: 24%, prior monotherapy: 42%. 226 patients have completed the first 48 weeks of treatment. The virological response rate was higher in group 1: 32% (36/114) than in group 2: 18% (20/112). The rate of virological response was higher among patients non-responders to prior monotherapy in group 1: 44% (21/48) than in group 2: 17% (8/47), and among patients with genotype non-1: 58% (21/36) in group 1 vs 24% (8/34) in group 2.

Conclusion: At week 48 of therapy the induction dose is more effective than the fixed dose in non-responders. The benefit of the induction regimen is more apparent in patients with prior IFN monotherapy and in those with genotype non-1 infection.

CONTROLLED TRIAL WITH PEGYLATED INTERFERON-ALPHA2B PLUS RIBAVIRIN RETREATMENT IN PATIENTS WITH CHRONIC HEPATITIS C NOT RESPONDING TO A PREVIOUS ANTIVIRAL TREATMENT WITH STANDARD INTERFERONS COMBINED WITH RIBAVIRIN

G. Teuber*, ¹B. Kallinowski, ²C. Niederau, ³H. Klinker, ⁴P.R. Galle, ⁵M. Zankel, ⁶S. Zeuzem, ¹

*Presenting Author, ¹Medizinische Klinik II, Frankfurt, Germany ²Innere Medizin IV, Heidelberg, Germany ³St. Josef Hospital, Oberhausen, Germany ⁴Luitpold Krankenhaus, Wuerzburg, Germany ⁵I. Medizinische Klinik, Mainz, Germany ⁶Essex Pharma, Muenchen, Germany

In interferon (IFN) non-responders with chronic hepatitis C retreatment with standard interferons combined with ribavirin showed sustained virologic response rates of 20-30%. Concerning the efficacy of antiviral retreatment in patients not responding to a previous treatment with standard interferons combined with ribavirin only limited data with conflicting results are available.

Aims: Evaluate the efficacy and safety of a retreatment with pegylated IFN- α 2b plus ribavirin in 240 patients (162 males, 78 females, mean age 45.5 years) not responding to previous antiviral treatment with standard interferons combined with ribavirin. Patients received pegylated IFN- α 2b 100 µg/week s.c. for 8 weeks followed by 50 µg/week s.c. for 40 weeks in combination with ribavirin 800 mg/d for 48 weeks. Treatment was discontinued in patients with detectable serum HCV-RNA after treatment week 24.

Results: A virologic end-of-treatment response was achieved in 25/240 (10.4%) patients while after a follow-up period of 24 weeks a sustained virologic response was observed in 15/240 (6.3%) patients. Patients infected with HCV genotype non-1 were more likely to respond to antiviral retreatment than patients infected with HCV genotype 1 (6.8% vs. 17%).

Conclusion: Antiviral retreatment with pegylated interferon- α 2b plus ribavirin in this flat and low dose showed only a limited therapeutic efficacy in patients with chronic hepatitis C not responding to previous treatment with standard interferons and ribavirin. In these patients, virologic response rates may be improved by administering pegylated interferon- α 2b and ribavirin bodyweight adapted or by the addition of other antiviral agents.

SHORT TREATMENT (14 WEEKS) WITH PEGYLATED INTERFERON ALPHA-2B AND RIBAVIRIN FOR THE TREATMENT OF HEPATITIS C GENOTYPE 2/3 INFECTION

O. Dalgard*, ¹K. Skaug, ²S. Ritland, ³B. Myrvang, ⁴K. Hellum, ⁵K. Bjoro, ⁶H. Bell, ¹

*Presenting Author, ¹Medical Department, Aker University Hospital, Oslo, Norway ²National Institute Of Public Health, Oslo, Norway ³Medical Department, Buskerud Hospital, Oslo, Norway ⁴Medical Department, Ullevaal University Hospital, Oslo, Norway ⁵Medical Department, Akershus University Hospital, Oslo, Norway ⁶Medical Department, National Hospital, Oslo, Norway

Aim: To determine the virological response rate after 14 weeks of combination treatment in patients with hepatitis C virus (HCV) genotype 2/3 who experience early HCV clearance.

Methods: In a multicenter trial 82 HCV RNA positive patients with genotype 2 or 3 have been included. All patients are treated with pegylated interferon alfa-2b 1, 5 µg/kg once weekly and ribavirin (800-1200 mg) daily. Treatment is stopped at week 14 in patients who are HCV RNA negative (Cobas Amplicor HCV monitor test, lower detection limit 100 copies/ml) at week 4 and 8. The remaining patients continue treatment until week 24.

Results: Eight weeks or more of combination treatment has been fulfilled in 63 patients. HCV RNA was negative at both week 4 and 8 in 45 (71%) and treatment is therefore discontinued at week 14 in these. The remaining 18 patients are receiving 24 weeks treatment. The preliminary results show that 80% of those who receive short combination treatment obtain sustained virological response 24 weeks after treatment stop (table).

Conclusion: This preliminary analysis suggests that in patients with HCV genotype 2/3 infection a high sustained response rate may be obtained after 14 weeks of combination treatment.

	4 weeks treatment (n=45)	8 weeks treatment (45)	End of Treatment (n=46)	10 weeks follow-up (n=34)	14 weeks follow-up (n=27)	24 weeks follow-up (n=20)
HCV RNA negative	(45 (100%))	45 (100%)	40 (98%)	30 (88%)	23 (85%)	16 (80%)

TREATMENT OF CHRONIC HEPATITIS C IN HIV INFECTED PATIENTS (PTS) WITH PEGYLATED INTERFERON ALPHA 2B (PEG-IFN) PLUS RIBAVIRIN (RBV) VERSUS PEGYLATED INTERFERON ALPHA 2B

A. Cargnel*, ¹E. Angeli, ¹A. Mainini, ¹A. Casella, ¹G. Gubertini, ¹R. Giorgi, ¹G. Orlando, ¹P.G. Duca, ²Coinfection Study (ICOS) Group, ³

*Presenting Author, ¹II Dept Infectious Diseases, L. Sacco Hospital, Milan, Italy ²Statistic Dept, University Of Milan, Milan, Italy ³, Italy

Background: In HIV pts chronic hepatitis C is more aggressive and, with the increase of survival after HAART, the mortality for end-stage liver disease is growing.

Aims: To study efficacy and tolerability of PEG-IFN + RBV vs PEG-IFN.

Methods: 135 pts on HAART with stable CD4+>300/mm³ and HIV-RNA<400 cp/ml and no prior therapy for HCV were randomized to receive: A) PEG-IFN 1.5 µg/Kg weekly plus RBV 800 mg daily; B) PEG-IFN 1.5 µg/Kg weekly for 48 ws. Statistical analysis was performed by GraphPad InStat.

Results: Baseline characteristics are listed below. To date, 67 pts ended 24 ws of therapy (32 group A, 35 group B). A virological response was observed in 24 (35.8%), 18 (56%) in group A and 6 in group B (17%)

($p=0.001$ Fisher's exact test), more frequently related to HCV genotypes 2-3 ($p=0.0045$ Fisher's exact test). A drop of at least 3 logs of HCV-RNA at 8 ws was significantly related to response at 24 ws ($p<0.0001$ Fisher's exact test). 14 pts completed 48 ws (9 in group A, 5 in group B): 11 (78.5%) had negative PCR, 9 in group A and 2 in group B ($p=0.0275$ Fisher's exact test). No significant difference in drops out, mostly occurred during the first month, was found between the 2 groups (29 group A, 22 group B): 24.4% pts dropped for side effects, the others for trial violations or compliance. No grade 3-4 toxicity occurred. A significant decrease of mean CD4+ cells at 24 ws was found in both groups (group A: mean 448, $p=0.02$; group B: mean 467, $p=0.04$ unpaired T test), an increase (1 log) of HIV-RNA only in 5 pts.

Conclusions: From our preliminary results, PEG-IFN plus RBV appears to be a promising choice of treatment even in HIV pts. Nevertheless, an adequate information and management of side effects and a strict monitoring are crucial for compliance.

BITRIPEG STUDY: TRIPLE THERAPY WITH PEGINTERFERON ALFA-2B PLUS RIBAVIRIN PLUS AMANTADINE VERSUS STANDARD THERAPY IN NON-RESPONDERS - AN INTERIM ANALYSIS

M. Maynard, S.N. Si Ahmed, F. Rozier, N. Benmakhlouf, V. Bourne-Branchu, C. Trepo*, French Multicenter Group,

*Presenting Author, Department Of Hepatology, Hotel-Dieu, Lyon, France

Background and aims: Triple antiviral therapy with interferon-alfa+ribavirin+ amantadine was suggested to increase sustained virological response rates in HCV non-reponder patients. This study was designed to evaluate the efficacy, side effects, quality of life (QoL) and safety of triple therapy with PegIntron+Ribavirin+Amantadine vs. double therapy with PegIntron+Ribavirin+Placebo in non-responders to standard interferon+Ribavirin therapy.

Methods: Multicenter, comparative, prospective, randomized, double blind study. Inclusion criteria were: elevated ALT, detectable HCV-RNA, and non-response to a previous cycle of IFN+Ribavirin therapy. Patients were randomized to receive PEG-IFN 1.5 $\mu\text{g}/\text{kg}/\text{week}$, Ribavirin 800-1200mg/day and either amantadine 200mg/day or placebo during 48 weeks. The primary endpoint of the study was HCV-RNA negativity 24 weeks after treatment discontinuation. Secondary endpoints included: histological benefit, ALT normalization, tolerability and compliance.

Results: Results are given for the whole population because the study is still ongoing. The 204 enrolled patients were predominantly males (73%), infected by genotype 1 (79%), and had a fibrosis score <F3 (65%). Among 86 patients at 48 weeks, 36% had undetectable HCV-RNA, 67% had normal ALT, 98% and 85% had an improved or stabilized histological activity and fibrosis scores, respectively. Furthermore, 63% had an improved or stabilized QoL. Among 55 patients at 72 weeks, sustained virological response rate was 26%.

Conclusion: Triple combination therapy is well-tolerated. QoL is maintained over time. Preliminary results suggest a potential benefit on sustained virologic response. The frequent improvement of biochemical and histological responses suggest that non-response can be often overcome. Furthermore, improved efficacy/tolerance ratio of triple combination makes a valuable option for maintenance therapy.

INTERFERON SENSITIVITY IN CHRONIC HEPATITIS C VIRUS GENOTYPE 4 INFECTION

W. Jessner*, ¹ M. Gschwantler, ² E. Formann, ¹ P. Steindl-Munda, ¹ H. Hofmann, ³ C. Mueller, ¹ P. Ferenci, ¹

*Presenting Author, ¹Department Of Internal Medicine IV, Gastroenterology And Hepatology, Vienna, Austria ²Department Of Internal Medicine IV, Krankenhaus Rudolfstiftung, Vienna, Austria ³Department Of Clinical Virology, University Of Vienna, Vienna, Austria

Background & Aims: Chronic HCV genotype 4 infection is considered as a difficult to treat disease like genotype 1. The initial sensitivity to IFN in genotype 1 as determined by viral kinetics identifies pts resistant to standard IFN/ribavirin or unlikely to achieve a sustained response to PEG-IFNalpha2a/ribavirin therapy.

Methods: Viral load was measured in 23 pts infected with genotype 4 using the Cobas Amplicor Monitor HCV Assay v2.0 before and 24h after 10 MU IFNalpha2b (AESCA-SPI, Austria) (days 0, 1), and before and during daily 5 MU IFNalpha2b (days 7, 8, 14, 20) administration. Thereafter, combination therapy (1-1.2g ribavirin daily, AESCA-SPI) with either 5MU IFNalpha2b every other day (n=5), 1.5 microg/kg PEG-IFNalpha2b (AESCA-SPI) weekly (n=7) or 180 microg PEG-IFNalpha2a (ROCHE, Austria) weekly (n=10) was given. Results: 24h log change after 10 MU IFNalpha (24lc10) was 1.34 (0.25-2.48; median-range) and after 5 MU IFNalpha was 0.99 (0.13-2.22, p<0.001). 24lc10 was 1.47 (0.40-2.48) for month 6 responder (n=18), 0.36 (0.25-0.57; p=0.006) for nonresponder (n=4) and highly predictive on ROC analysis (AUC=0.867; p=0.007). Currently 6 responder have completed follow-up, one relapsed after stopping treatment at month 8 (24lc10=1.88), one relapsed after the full 12 month course (24lc10=0.44), and 4 became sustained responder (24lc10=1.59 [1.26-1.91])

Conclusion: Primary interferon resistance as in genotype 1 occurs in genotype 4 as well although at a lower rate. Overall response to IFN is therefore significantly better as in genotype 1. A 24 hour response to standard interferon has high predictive power for on treatment response as in genotype 1.

EARLY VIROLOGIC RESPONSE (EVR) AT WEEK 8 IS MORE PREDICTIVE OF SUSTAINED RESPONSE (SR) TO PEGYLATED COMBINATION THERAPY THAN AT WEEK 12

M. Martinot-Peignoux*, ¹ L. Comanor, ² M.P. Ripault, ¹ N. Boyer, ¹ C. Castelnau, ¹ N. Guily, ¹ D. Hendricks, ³ P. Kipnis, ³ P. Marcellin, ¹

*Presenting Author, ¹INSERM U481 And Service D'hepatologie, Clichy, France ²Medical Consultant, Palo Alto Ca, USA ³Bayer Diagnostics, Emeryville Ca, USA

Aim: This study was to assess the predictive value of EVR in patients receiving combination therapy with PEG-IFN plus RIBA.

Methods: 81 patients: 43 naive and 38 previously treated (PT), treated with the combination of Peg-IFN alpha 2b + RIBA were studied. Serum HCV RNA was measured at baseline, weeks 1, 2, 4, 8, and 12, end of treatment and 24 weeks after treatment by VERSANT HCV 3.0 (bDNA) assay and VERSANT HCV RNA Qualitative Assay (HCV TMA). EVR was defined as = 2 log drop of HCV RNA with bDNA or undetectable HCV RNA with TMA during the first 12 weeks of therapy.

Results: Kinetic slope of HCV RNA in SR was faster in naive than in PT patients. Positive Predictive Value (PPV) of SR according to EVR was 96%, 86%, 80% and 80% in naive and 71%, 67%, 60% and 63% in PT at week 2, 4, 8 and 12, respectively. Negative Predictive Value (NPV) of SR according to EVR was 25%, 9%, 0% and 0% in naive and 19%, 20%, 18% and 17% in PT, at week 2, 4, 8 and 12, respectively. PPV of SR according to TMA was 100%, 94%, 85% and 88% in naive and 0%, 94%, 100% and 86% in PT at week 2, 4, 8 and 12, respectively. NPV of SR according to TMA was 66%, 52%, 42% and 17% in naive and 48%, 41%, 28% and 23% in PT, at week 2, 4, 8 and 12, respectively. The more accurate predictive values for SR were TMA negative at week 4 or EVR at week 8.

Conclusions: Prediction of SR assessed by = 2 log drop (bDNA) or undetectable (TMA) HCV RNA might

be done as early as week 2 in naïve patients and as early as week 4 in PT patients. Prediction of no SR is optimal at week 8 in naive and somewhat less accurate in PT patients. Therefore treatment status should be considered when assessing patients response to therapy.

THE IMPACT OF STEATOSIS ON BASELINE CHARACTERISTIC AND END OF TREATMENT RESPONSE FOR CHRONIC HEPATITIS (C) GENOTYPE 4 PATIENTS TREATED WITH INTERFERON

G. Esmat*, ^{1, 3} M.K. Mohamed, ^{2, 3} M. Abdel Hamid, ³ K. Zalata, ⁴ H. Khatib, ⁶ M. El Batanony, ⁵ A.M. Abouzied, ^{3, 7} M. El Raziky, ^{1, 3} A.M. Shaheen, ^{3, 7} A. Ismail, ⁷ G.T. Strickland, ^{3, 8} A. Fix, ^{3, 8} M. Sjogren, ⁹

*Presenting Author, ¹Tropical Medicine Dept, Cairo Univ, Cairo, ²Epidemiology And Preventive Medicine Dept, Ain Shams Univ, Ain Shams, ³Hepatitis C Research Project, UMB, ⁴Pathology Dept, Mansora Univ, Mansora, ⁵Pathology Dept, National Liver Institute, Menofeyah Univ, Menofeyah, ⁶Pathology Dept, Cairo University, Cairo, ⁷National Hepatology And Tropical Medicine Research Institute, Egypt ⁸Epidemiology And Preventive Medicine Dept, Univ Of Maryland, MD, ⁹Gastroenterology Dept, Walter Reed Army Hospital, Washington DC, USA

Background: Steatosis is a common histological feature with patients of HCV infection, particularly in genotype 3. Its significance is incompletely understood and no data is available about the effect of steatosis on genotype 4 patients.

Aim of Study: To evaluate whether the presence and severity of steatosis affect the baseline presentation on chronic HCV genotype 4 patients and their response to Interferon.

Methods: 200 naïve patients with chronic HCV infection were randomized for treatment with either Interferon a 2b + Ribavirin or Peg-Interferon a 2b + Ribavirin. Liver biopsy specimens were blindly evaluated for the presence and severity of steatosis. Steatosis was recorded as a percentage of hepatocytes affection and assigned a grade based upon this percentage, grade 0 for no steatosis, grade 1 for < 30%, grade 2 for 30-60%, grade 3 for > 60%. Genotype, viral load, ALT, serum glucose, BMI were also evaluated.

Results: From 200 patients, 48% had grade 0 steatosis, 34% had grade 1, 14% had grade 2 and 4% had grade 3. Most of the patients (87%) had genotype 4. There was no correlation between genotype, viral load, fibrosis, ALT with steatosis. While BMI was correlated to steatosis, end of treatment response was related to presence of steatosis, normal ALT was noticed in 83% of grade 0, 64% of grade 1 and 62% of grade 2 and 3. Negative PCR HCV was found to be 64% of grade 0, 64% of grade 1, 53% of grade 2 and 3. In those receiving Peg-Interferon a 2b, PCR HCV was found to be 70% of grade 0, 77% of grade 1 and 42% of grade 2 and 3.

Conclusions: Steatosis has no relation with baseline characteristics of chronic HCV genotype 4. Biochemical response is affected by steatosis. Virological response in patients receiving Peg-Interferon a 2b is affected by Steatosis severity.

PREFERENCE-BASED QUALITY-OF-LIFE VALUES IN PATIENTS WITH CHRONIC HEPATITIS C: RESULTS FROM THE GERMAN HEPATITIS C QUALITY-OF-LIFE STUDY

U. Siebert*, ^{1, 2}W. Greiner, ³ U. Ravens-Sieberer, ⁴ G. Sroczynski, ¹ J.B. Wong, ⁵ J.M. Graf von der Schulenburg, ³ M. Bullinger, ⁶ S. Rossol, ⁷ German Hepatitis C Model (GEHMO) Group,

*Presenting Author, ¹Harvard School Of Public Health, Boston, USA ²University Of Munich, Munich, Germany ³University Of Hanover, Hanover, Germany ⁴Robert Koch-Institute, Berlin, Germany ⁵Tufts University School Of Medicine, Boston, USA ⁶University Of Hamburg, Hamburg, Germany ⁷University Hospital Mannheim, Mannheim, Germany

Introduction: Patients with chronic hepatitis C (CHC) experience different health states and quality of life (QoL) depending on the severity of the disease as it progresses. Objective: To assess preference-based QoL values (utilities) for clinical and histological health states in patients with CHC.

Methods: A total of 428 patients with CHC participated in a cross-sectional, interview-based study using the utility instruments rating scale (RS) and EuroQoL (EQ-5D). Current clinical and histological health status was assessed and assigned to an ordinal scale representing ascending severity of disease. Rating scale was transformed by the Torrance transformation. Multivariate stepwise regression with a log-transformed outcome was used to calculate utilities for the health states adjusted for age, gender, viral status, co-morbidity, and short-term effect of current antiviral medication.

Results: Utility values based on EQ-5D ($r=0.13$; $p<0.019$) and RS ($r=0.24$; $p<0.001$) showed significant correlation with the severity of disease scale. Overall, EQ-5D resulted in lower utilities than RS. Depending on health state and instrument, utilities ranged from 0.92 (mild hepatitis, RS) to 0.72 (hepatocellular carcinoma, EQ-5D). Short-term utility reduction during combination therapy with (peg) interferon and ribavirin was 15% ($p<0.001$). EQ-5D and RS were highly and significantly correlated ($r=0.64$, $p<0.001$), suggesting that the results are robust.

Conclusions: This study suggests that severity of disease is reflected by EQ-5D and rating scale, and both are feasible and robust instruments for assessing patient preferences regarding quality of life. These results can be used in cost-effectiveness analyses in studies of patients with chronic hepatitis C.

EFFECTIVENESS AND COST-EFFECTIVENESS OF INITIAL ANTIVIRAL TREATMENT IN PATIENTS WITH CHRONIC HEPATITIS C. A GERMAN HEALTH TECHNOLOGY ASSESSMENT AND DECISION ANALYSIS COMMISSIONED BY THE GERMAN FEDERAL MINISTRY OF HEALTH

U. Siebert*, G. Sroczynski,

**Presenting Author, Institute Of Medical Informatics, Biometry, And Epidemiology, University Of Munich, Munich, Germany*

Objective: The purpose of this health technology assessment (HTA) commissioned by the German Agency for HTA at the German Federal Ministry of Health was to systematically review the evidence on effectiveness and cost-effectiveness of initial antiviral treatment (AVT) for chronic hepatitis C (CHC) and apply these data in the context of the German health care system.

Methods: A systematic literature search was conducted to identify randomised controlled trials (RCTs), meta-analyses, and HTAs that evaluated initial AVT for CHC. The German Hepatitis C Model (GEHMO) -- a decision-analytic Markov model -- was used to determine long-term morbidity, life expectancy, quality of life, and costs of different treatment strategies. Model parameters were derived from German databases, international RCTs, and a Cochrane Review. Results: Overall, 9 RCTs, 2 meta-analyses, 7 economic evaluations, and 1 HTA met the inclusion criteria. These studies indicate that combination therapy with peginterferon plus ribavirin (PCOM) produced highest sustained virological response rates (54-61%), followed by interferon plus ribavirin (SCOM) with 38-54%, and interferon monotherapy (MONO) with 11-21%. Based on international cost-effectiveness studies, SCOM is cost-effective compared to MONO. No published articles were available for cost-effectiveness of PCOM. In our decision analysis, these findings were confirmed and the discounted incremental cost-effectiveness ratio for PCOM was 8, 200 Euro per quality-adjusted life-year gained.

Conclusions: This HTA suggest that initial combination therapy prolongs life, improves quality of life, and is cost-effective in patients with CHC. Combination of peginterferon and ribavirin is the most effective and efficient treatment strategy among the examined options.

OBSERVATIONAL STUDY OF PATIENTS TREATED FOR CHRONIC HEPATITIS C IN FRANCE

F. Roudot-Thoraval*, ¹ P. Couzigou, ² J.J. Raabe, ³ H. Desmorat, ⁴ P. Marcellin, ⁵

*Presenting Author, ¹Sante Publique, Hopital Henri Mondor, Creteil, ²Hepato-Gastroenterologie, Hopital Haut-Leveque, Pessac, ³Hepato-Gastroenterologie, CHR De Metz, Metz, ⁴Clinique Du Parc, Toulouse, ⁵Hepatology, Hopital Beaujon, Clichy, France

Objective: of this observational study was to evaluate medical practices for the treatment of chronic hepatitis C, and to assess the observance, tolerance and efficacy of treatment outside clinical trials.

Methods and results: a sample of 50 specialists working in various settings participated in the study. All consecutive patients who were prescribed authorized antiviral drugs were enrolled. Demographic, epidemiological and virological data were collected before treatment; follow up was made according to the habits of each prescriber and included information on acceptability of the treatment, dose modifications and their motive. Between April 1st and December 31st 2001, 578 patients were enrolled.

The epidemiological, virological and histological features of this group were similar to those patients usually treated in France. Fifty-seven percent of patients were naive of treatment, 16% were relapsers and 27% were non responders. In 93% of cases, treatment consisted of Peginterferon α -2b (PEG-IFN) and ribavirine at recommended doses: on average 1.4 μ g/kg of PEG-IFN and 13 mg/kg of ribavirine (16 to 11 mg/kg according to weight), irrespective of gender, genotype and the existence of a previous treatment. All patients have been followed at least 24 weeks. Currently, 26 patients (4.5%) have withdrawn treatment; 110 (19%) patients have needed a dose reduction of PEG-IFN and/or ribavirine. The acceptability of treatment was good for 36% of patients, moderate or poor for 64% of patients. The latter were more often women (44 vs 34%, $p=0,02$), they were older (48, 8 vs 44, 6 ans, $p=0,001$), for an equivalent dose of PEG-IFN and ribavirine. Nevertheless, a dose reduction was prescribed in only 32% of patients with moderate or poor tolerance, these patients receiving an average higher initial dose of PEG-IFN (1.5 vs 1.4 μ g/kg, $p=0.01$). Virological response under treatment is now available for 299 patients: HCV-RNA is undetectable in 199 of them (66.6%, IC95% 61.2-71.9).

Conclusion: This observational study shows that 1) most patients are treated according to recommendations 2) Early withdrawal of combination therapy remains rare, 3) Initial regimen is often continued despite moderate or poor tolerance, what may be valuable to reach virological response.

IS TREATMENT OF CHRONIC HEPATITIS C IN PATIENTS UNDER METHADONE MAINTENANCE FEASIBLE? A PROSPECTIVE; CONTROLLED STUDY

S. Mauss*, ¹ F. Berger, ¹ J. Goelz, ² B. Jacob, ³ S. Guenther, ¹

*Presenting Author, ¹Center For HIV And Hepatogastroenterology, Duesseldorf, Germany ²Praxiszentrum Kaiserdamm, Berlin, Germany ³Municipal Methadone Outpatient Clinic, Duesseldorf, Germany

Background: Systematic data assessing the treatment of patients with chronic hepatitis C under methadone maintenance are rare. In contrast intravenous drug users represent the most relevant patient population with newly infected young individuals in the western world.

Methods and results: In a prospective study 100 patients, 50 under methadone and 50 control patients were matched for sex, age, hcv-genotype, and hcv-rna. In each group 44 patients were male, hcv-genotype 1 or 4 were present in 29 patients (58%) and genotype 2 or 3 in 21 patients (42%). Median age was 35

years (methadone) and 40 years (control). The median hcv-rna was 556.000 IU/ml (methadone) and 708.000 IU/ml (control). Treatment with pegylated interferon alfa-2b (1, 5 µg/kg qw) and ribavirin (800 - 1200 mg bid) lasted 6 (genotype 2, 3) or 12 months (genotype 1, 4). Median time on stable methadone maintenance was 21 months. At the end of treatment hcv-rna <600 IU/ml was reached in 21/43 methadone patients (49%) and in 32/45 (71%) controls (p=0.049, lost to follow up equals failure analysis). Discontinuation due to non-compliance or side effects was 18/43 in methadone patients (42%) and 8/45 control patients (18%) (p=0.019). Laboratory markers (e.g. ALT, leukocytes, haemoglobin, platelets) were not different between methadone arm and control. No serious psychiatric adverse event occurred in both arms.

Conclusion: Pegylated interferon and ribavirin seems reasonably safe and sufficiently effective in patients on methadone maintenance. The lower efficacy in methadone patients is most probably due to a lower adherence. But the end of treatment result is still close to the results of the pivotal study which led to the approval of pegylated interferon alfa-2b and ribavirin combination therapy (Manns, Lancet 2001;358: 958-965).

HIGH SVR RATE IN HCV PTS WITH NORMAL OR INCREASED ALT: A CONTROLLED STUDY WITH IFN ALPHA 2B AND RIBAVIRIN

A. Mangia*, ¹M. Piattelli, ¹O. Vuturo, ²G. Spinzi, ³O. D'Apolito, ¹A. Iacobellis, ¹G. Minoli, ³G. Montalto, ²A. Andriulli, ¹
*Presenting Author, ¹Gastroenterology Division Hospital 'CSS' San Giovanni, Rotondo, Italy ²Internal Medicine University, Palermo, Italy ³Gastroenterology Division Hospital 'Valduce', Como, Italy

Background: Current guidelines do not recommend treatment for HCVRNA+ve pts with normal ALT. However fibrosis has been detected in 0-22% of cases and advanced disease in 5-10%.

Methods: Among 140 pts with normal ALT we selected 35 HCV RNA+ve with fibrosis (Group 1), and matched for sex, age, stage, and genotype (1: 3) with 105 with raised ALT. Both groups were treated with IFN alpha2b tiw and ribavirin 1000-1200 mg/die for 12 mos.

Results: ETR were 71.4%(95% C.I.56.4-86.3) in Group 1 and 53.3% (95% C.I.43.7-62.8) in Group 2 (p=0.03). 8.6 and 3.8% respectively, relapsed. SVR was observed in 22 pts from Group 1 (62.8%; 95% C.I. 46.8-78.1) and 52 (49.5%; 95% C.I.39.9-59.1) from Group 2 (p=0.11). At 3 months, PPV of a positive HCVRNA for SVR were 100% and 96% and NPV 88% and 72.2% in Group 1 and 2, respectively. At multivariate analysis genotype non 1 was the only predictive factor for SVR.

Conclusions: Pts with normal ALT have a response to combination tx comparable to that of pts with raised ALT. Stage 1 of fibrosis rather than ALT levels might be the criterion to treat these pts.

CONTROLLED STUDY OF INTERFERON A-2B (IFN) PLUS RIBAVIRIN (RIB) IN PATIENTS WITH CHRONIC HEPATITIS C (CHC) 'NON-RESPONDERS' TO IFN

R. Moreno-Otero*,

*Presenting Author, ¹Spanish Association For Study Of The Liver (AEEH, Asociacion Espanola Para El Estudio Del Hgado). Multicentre Group For The Study And Management Of Chronic Hepatitis C In Non-Responders, Madrid, Spain ²Liver Unit. Hospital De La Princesa, Madrid, Spain

BACKGROUND: Combination therapy with IFN plus RIBAVIRIN at a standard dose in CHC non-responders to previous treatment with IFN, induces a sustained response (SVR) in nearly 16% of patients. No extensive

studies increasing IFN dose with the aim of obtaining a higher response rate exist.

OBJECTIVES: To compare the efficacy and safety of two different regimen doses of Interferon α -2 β : 5 MU IFN tiw (group A) Vs. 3 MU IFN tiw (Group B) in combination with Ribavirin.

METHODS: Prospective, randomised study using blocks. The analysis included virologic and biochemical response rates at months 6 (to define non-responders) and 12 (to define ETR) of treatment, and at month 6 of follow-up (to define SVR). The analysis was by intention to treat and was measured in terms of normal serum transaminase values and negative HCV RNA.

Number of patients: 471	DEMOGRAPHICS	TREATMENT	FOLLOW-UP (MONTH 6)	SVR by INTENTION TO TREAT
		MONTH12 (ETR)	SVR	
Group A: (N=240)	Age (mean \pm S.D.): 42 \pm 9.6 years % Male sex: 80.4% % Genotype 1: 85.9%	80/220 (36.4 %)	57/219 (26.0 %)	57/240 (23.7%)
Group B: (N=231)	Age (mean \pm S.D.): 42 \pm 9.8 years % Male sex: 73.1% % Genotype 1: 83.5%	56/216 (25.9 %)	35/209 (16.7 %)	35/231 (15.1%)
P(Chi-square)		P=0.019	P=0.019	P=0.019

RESULTS:

SAFETY: The combination therapy was well tolerated in both groups.

CONCLUSION: These results demonstrate a statistical significantly higher SVR rate in patients in group A (23.7% vs. 15.1%). At the same time, tolerability to the combination therapy was similar in both groups using different doses of IFN. For a future therapeutic approach, it can be speculated that combined therapy using higher doses of pegylated IFN or, possibly, prolonged treatments could add further benefits for non-responders.

IMMUNOLOGICAL, VIROLOGICAL AND CLINICAL LONG-TERM FOLLOW-UP AFTER INTERFERON THERAPY OF ACUTE HEPATITIS C INFECTION

J. Wiegand*, ¹ H.L. Tillmann, ¹ E. Jackel, ¹ M. Cornberg, ¹ M. Dietrich, ² H. Hinrichsen, ³ W.P. Fritsch, ⁴ J. Kroger, ⁵ N. Aslan, ¹ A. Kubitschke, ¹ M.P. Manns, ¹ H. Wedemeyer, ¹

*Presenting Author, ¹Dept. Of Gastroenterology, Hepatology And Endocrinology, Hannover Medical School, Hannover, Germany

²Bernhard-Nocht Institut, Hamburg, Germany ³Medizinische Klinik, Universitat Kiel, Kiel, Germany ⁴Medizinische Klinik II, Universitat Des Saarlandes, Saarlandes, Germany ⁵Städtisches Krankenhaus, Hildesheim, Germany

Background: Acute hepatitis C infection can be successfully treated with interferon-alfa monotherapy (Jäckel, NEJM 2001, 345: 1452). We report the immunological, virological and clinical long-term outcome of 29 patients who had been treated with interferon alfa-2b. Median time of follow-up after the end of treatment was 124 weeks.

Importantly, HCV-RNA was not detectable in any of the serum samples tested during follow up. Throughout follow-up there were no clinical or biochemical signs of hepatitis. Furthermore, quality of life scores (SF36, Fatigue Impact Scale) were better in the study cohort as compared to chronic hepatitis C controls.

Titers and specificity of anti-HCV-antibodies were investigated over time. While NS3 was recognized in nearly all patients, anti-E2 and anti-NS5 antibodies were barely detectable. Interestingly, antibody titers

significantly increased during the first 4 weeks of therapy and then continuously declined thereafter in all patients tested.

Finally, frequency and function of HCV-specific T cells were investigated by ELISPOT- and Proliferation assays. HCV-specific CD4+ T cell responses targeted against structural as well as non-structural antigens were found in three fourth of the patients and these responses were significantly stronger than in chronically infected controls. The frequency of CD8+ T cells was lower and only 33% of the HLA-A2-positive patients tested positive for at least 2 peptides.

Conclusions: Interferon alfa therapy leads to sustained clinical remission after acute hepatitis C which is associated with improved quality of life. Specificity and strength of anti-HCV humoral and cellular immune responses are regulated differentially after recovery. While antibody titers do decline, HCV-specific T cell responses seem to be maintained in the majority of patients potentially contributing to long-term control of low levels of residual virus.

PREDICTIVE VALUE OF EARLY HCV RNA QUANTIFICATION FOR SUSTAINED RESPONSE IN NON RESPONDERS RECEIVING DAILY INTERFERON AND RIBAVIRIN THERAPY

P. Trimoulet*, ¹ V. de Ledinghen, ² J. Foucher, ² L. Castera, ² H. Fleury, ¹ P. Couzigou, ²

*Presenting Author, ¹Laboratoire De Virologie, Hopital Pellegrin, Bordeaux, France ²Service D'Hepatogastroenterologie, Hopital Haut Leveque, Pessac, France

Aim: We evaluated the prognostic value of early HCV-RNA load among non responders (NR) to previous interferon (IFN) therapy treated with daily IFN and ribavirin.

Methods: 106 NR (83 men), mean age 44.8±11 yrs, were treated with IFN- α 2b 3MU daily during 24W followed by 3Mux3/W during 24W plus ribavirin 1 to 1.2 g/day during 48W. HCV-RNA was quantified by Versant HCV RNA 3.0 assay (Bayer Diagnostics; sensitivity 615 IU/ml) at baseline, W1, W4 and W12. The predictive values of the baseline and the change in viral load at W1, 4, and 12 for sustained virological responses (SVR) were analyzed using ROC curves as well as predictive values of HCV-RNA<615 IU/ml or >2-log₁₀ drop from baseline by W1, 4, and 12 for SVR.

Results: 32 patients (30.2%) were SVR (qualitative HCV-RNA<50 IU/ml at W72). The highest area under the curve was obtained at W4. Patients with more than 334, 173 IU/ml at W1 or more than 77, 738 IU/ml at W12 had no chance (negative predictive value (NPV) 100%) to achieve a SVR. HCV-RNA level>615 IU/ml had a NPV of 74%, 84% and 97% at W1, W4 and W12, respectively. The NPV of <2-log₁₀ drop in combination with HCV-RNA>615 IU/ml by W1, W4 and W12 were 73%, 96% and 97%, respectively.

Conclusion: Non response might be predicted as early as W4 or W12 in NR treated with daily IFN and ribavirin. This information may be useful for the management of previous NR patients retreated with PEG-IFN (kinetics similar to daily IFN).

COMPLIANCE AND EFFECT OF TREATMENT FOR CHRONIC HEPATITIS C (CHC) IN INTRAVENOUS DRUG USERS (IVDUS)

G. Robaey*, ¹ H. Van Vlierberghe, ² C. Mathei, ³ M. Van Ranst, ⁴ L. Bruckers, ⁵ F. Buntinx, ^{3, 6} The Members Of The BASL Steering Committee Benelux Study Group,

*Presenting Author, ¹Department Of Gastroenterology And Hepatology, ZOL, Genk, Belgium ²Department Of Gastroenterology

And Hepatology, Ghent University Hospital, Ghent, Belgium ³Department Of General Practice, University Of Leuven, Leuven, Belgium ⁴Laboratory Of Clinical And Epidemiological Virology, Department Of Microbiology And Immunology, Rega Institute And University Hospitals, University Of Leuven, Leuven, Belgium ⁵Center For Statistics, Limburgs Universitair Centrum, Diepenbeek, Belgium ⁶University Of Maastricht, Maastricht, Netherlands

BACKGROUND: There is reluctance to treat IVDUs infected with CHC because of presumed lower compliance and response to antiviral therapy.

AIMS: We studied if the compliance and response to treatment were lower in IVDUs compared to non-IVDUs.

METHODS: Complete response (CR), compliance and SVR were measured in a subanalysis of a randomised clinical trial evaluating the efficacy of an induction dose of IFN a-2b (daily at 5MU SC; 8 weeks) (group A) as compared to IFN a-2b at 5MU SC thrice weekly (group B), followed by the standard dose of IFN a-2b (3MU thrice a week) in previously untreated CHC patients. In both groups, ribavirin was added at week 5. Treatment lasted 48 weeks. CR was defined as: an ALT within normal limits and serum PCR negative at the end of therapy. Compliance was determined as presentation for PCR determination at the end of treatment. SVR was determined as an undetectable HCV RNA level at the end of a 6 month follow-up period.

RESULTS: Of 406 patients, 98 (24%) were IVDUs (49.0% included in arm A). Noncompliance in IVDUs was not different from non-IVDUs. CR was better in IVDUs than in non-IVDUs. However, when controlling for genotype the CR was not different (RR=0.89; 95%CI=0.68 –1.16). Controlling for treatment arm, age, sex, presence of cirrhosis, viral load didn't change these results. There was no difference in SVR between IVDUs and non-IVDUs.

CONCLUSIONS: In this study IVDUs showed the same compliance and response to treatment with IFN and ribavirin compared to other patients with CHC viral infection after adjusting for genotype. Therefore, it is not longer justifiable to withhold treatment to chronic hepatitis C patients who use intravenous drugs.

LIVER FIBROSIS REGRESSES BETTER WITH PEGINTERFERON ALPHA AND URSODEOXYCHOLIC ACID TREATMENT THAN SPONTANEOUS RECOVERY

I. Tasci*, ¹ M.R. Mas, ¹ S.A. Vural, ² N. Mas, ³ M. Serdar, ⁴ B. Comert, ¹ G. Alcigir, ² I.H. Kocar, ¹

*Presenting Author, ¹Internal Medicine, Gulhane Medical School, ²Pathology, Veterinarian Faculty Of Ankara University,

³Anatomy, Hacettepe University, ⁴Biochemistry, Gulhane Medical School, Ankara, Turkey

Background: Fibrosis and cirrhosis are common complications of chronic liver diseases. An imbalance between fibrogenesis and fibrolysis results in scarring of the liver parenchyma.

Aim: To investigate the possible antifibrotic effectiveness of a newly modified interferon molecule peginterferon a2b (PEG-IFN) which has better antiviral activity and ursodeoxycholic acid (UDCA). Liver fibrosis was established on 60 male Sprague Dawley rats with CCl₄ in 12 weeks.

After cessation of CCl₄ Group I was left for spontaneous recovery. Group II was treated with PEG-IFN 1.5mg/kg/week, Group III with UDCA 25 mg/kg/day and, Group IV with combination of both drugs.

All rats were killed at week 16. Histopathologic fibrosis scores, tissue hydroxyprolin, TIMP-1 and MMP-13 levels were determined. Apoptosis was detected by TUNEL staining. Fibrosis scores were lower in both Group II, III and IV than Group I (p<0.05, p<0.05, p<0.007, respectively). Tissue hydroxyprolin levels were significantly decreased in Group II, III and IV when compared to Group I (p<0.05, p=0.00, p<0.001, respectively). Lower liver TIMP-1 and higher MMP-13 levels were measured in Group II, III, and Group IV

than Group I ($p=0.007$, $p=0.05$, $p<0.001$ for TIMP and $p<0.001$, $p=0.02$, $p<0.001$, for MMP, respectively). Apoptosis was significantly increased in Group II, III and IV when compared to Group I ($p<0.001$, $p<0.05$, $p<0.05$, respectively). There was significantly higher apoptosis in Group II than III and IV ($p<0.06$, $p<0.05$, respectively).

Conclusion: In conclusion, treatment with both peginterferon a2b and ursodeoxycholic acid improves CCL4 induced rat liver fibrosis. Significantly higher effects can be obtained using these agents in combination.

A RANDOMIZED CONTROLLED TRIAL OF PEGYLATED-INTERFERON ALPHA-2B + RIBAVIRIN VS INTERFERON ALPHA-2B + RIBAVIRIN IN HIV CO-INFECTED PATIENTS

S. Pol*, C. Perronne, F. Carrat, F. Banisadr, P. Morand, F. Lunel, E. Rosenthal,

* *Presenting Author, ANRS HC02 - Ribavic, Paris, France*

Background: HCV-related morbidity and mortality is increasing in HIV-infected subjects and treatment of hepatitis C became a significant issue.

Aim: To compare the safety and efficacy of a 48 week-course of the standard (IFNalpha2b: 3 MU x3/w, n=210) to the pegylated (PEG-IFNalpha2b: 1.5 mg/kg x1/w, n=206) interferon + ribavirin combination (800mg/d, > 12 mg/kg/d).

Methods: A randomized trial in HCV-RNA-positive pts with chronic hepatitis, CD4 > 200 and stable HIV-RNA.

Results: The 416 pts (40 y, 73% M, 79% IVDU) were given HAART in 80%; they had a mean CD4 cell count of 515 + or - 228/ml, HIV RNA < 200 in 60% (mean viral load in others: 3.48 + or - 0.8 logs). Mean Metavir score was A 1.8 + or - 0.7, F 2.3 + or - 1.0; 39% of pts had F3-F4. A EOT virologic response was observed in 27% of IFN group pts and 44% of PEG group pts ($p=0.009$), varying with genotypes: 19% in 1 and 4 vs 57% in 2 and 3. Treatment was discontinued in 124 pts (30%) and severe adverse events occurred in 99 (24%) (42 IFN & 57 PEG- $p=0.08$). A significant decrease ($p < 0.001$) was observed at the early stage of treatment (W12) in Hb, lymphocytes and more marked with PEG-IFN for neutrophils ($p=0.0035$) and platelets ($p=0.02$).

Conclusions: A 48 weeks course of PEG-IFNalpha2b + ribavirin achieves more frequently a therapeutic virologic response than the standard combination in co-infected patients and appears as the reference therapy.

HIGH RISK OF MITOCHONDRIOPATHY IN HIV/HCV CO-INFECTED PATIENTS UNDER CONCOMITANT DDI/D4T AND INTERFERON (STANDARD OR PEGYLATED IFN) /RIBAVIRIN TREATMENTS

S. Pol*, F. Carrat, T.R. Hor, J. Deshayes, F. Banisadr, E. Rosenthal, C. Perronne,

* *Presenting Author, ANRS HC02 Group; ANRS, Paris, France*

Background: To prospectively evaluate the incidence of mitochondrial toxicity events (MTE) in HIV/HCV infected pts under HAART and ribavirin. Methods: Mitochondrial toxicity was defined by the occurrence of hyperlactatemia (3.6-7.4 mmol/l) or acute pancreatitis in 416 HIV/HCV infected pts randomized in a trial comparing a 48 week-course of std (3 MU x3/w) or pegylated IFNalpha2b (1.5 mcg/kg/w) + ribavirin 800mg/d combination.

Results: 80% had HAART for a mean of 6.3 + or - 3.0 y: 26% with ddl, 55% with d4T and 73% with 3TC. 60% had undetectable viral load < 200 and mean HIV viral load was 3.5 + or - 08 log copies/ml for the others. Mean CD4 cell was 515 + or - 525. From W8 to W48, hyperlactatemia occurred in 10 and acute pancreatitis in 4 pts, both in 1. Twelve of the 13 pts were under d4T or ddl for 6 + or - 2 y before starting HCV treatment. MET was observed in 22% of patients receiving both ddl and d4T, 7% of those with ddl without d4T and 1% of those without ddl; the odd-ratios were 24 (p< 0.001), 6.6 (p=0.08) and 0.9 (p=0.88), respectively. In multivariate analysis, an increased risk was found for regimen containing ddl OR: 18.3 (95% CI: 3.9-85) ; p=0.0002 but not for d4TOR: 2.6 (91%CI: 0.7-10) ; p=0.17.

Conclusion: 16% of the pts with ddl and IFN ribavirin develop a MTE indicating the need for a careful choice of antiretroviral drugs and a closer follow-up when HIV/HCV treatments including ribavirin are given

PRELIMINARY RESULTS OF NAIVE COMBINATION THERAPY WITH 12KDA PEG-IFN a-2B AND RIBAVIRIN IN RECURRENT HEPATITIS C AFTER LIVER TRANSPLANTATION (LT)

B. Lavezzo*, ¹ A. Franchello, ² A. Smedile, ¹ D. Cocchis, ² E. David, ³ V. Ghisetti, ⁴ M. Torrani, ¹ A. Ricchiuti, ² M. Salizzoni, ² M. Rizzetto, ¹

*Presenting Author, ¹Department Of Gastroenterology, Molinette Hospital, Turin, Italy ²Department Of Liver Transplant Surgery, Molinette Hospital, Turin, Italy ³Department Of Pathology Division, Molinette Hospital, Turin, Italy ⁴Department Of Virology Division, Molinette Hospital, Turin, Italy

Background: the effectiveness (sustained virological response, SVR) of combination therapy (CT) with interferon and ribavirin in patients (pts) with recurrent hepatitis C after LT is low (10-30%). Pegylated IFN have increased SVR in non-transplanted pts with chronic hepatitis C.

Aim: to investigate tolerance, safety and efficacy of 12kDa PEG-IFN a-2B and ribavirin in recurrent hepatitis C after LT. Methods: 16 naive pts, mean age 54 ys (34-62), 81% males 62% genotype 1, with recurrent hepatitis C after LT, histology at baseline: acute hepatitis in 3 pts chronic hepatitis in 13, mean grading 7/18 (4-12), mean staging 2/6 (1-3), were treated with PEG-IFNa-2B 1 mcg/kg weekly plus ribavirin 800 mg/die for 12 months (mo). Median time LT to treatment was 10 mo (3-74). The primary end-points are HCV-RNA negative (by PCR, Monitor Roche) at end of treatment (ETVR) and at 24 week of follow-up (SVR).

Results: seven pts (44%) discontinued therapy for side effects at a median of 4 mo (1-6) since initiation: 2 pts before 3 mo, 5 before 6 mo. The causes of discontinuation were: important psychiatric or influenza-like symptoms in 5 pts; 2 pts developed severe jaundice (with negative HCV-RNA). Fourteen (88%) of pts need peg-IFN dose reduction for leukopenia (< 2500 109/l); but none of pts who continued therapy >3 mo tolerated the full dosage. ETVR was obtained in 7/16 pts (43, 7%), 3 of them with normal ALT level. Follow-up to evaluate SVR is on going.

Conclusions: PEG-IFN a-2B can improve ETVR and hopefully SVR in recurrent hepatitis C after LT. Tolerance is lower than conventional CT and the dose reduction may influence efficacy. Longer follow-up and close monitoring side effects will determine the real efficacy or limitations of current available therapy.

TREATMENT OF NAÏVE HEPATITIS C RECURRENCE (HCV-R) IN LIVER TRANSPLANT RECIPIENTS WITH PEGYLATED INTERFERON ALPHA-2B AND RIBAVIRIN

G.W. Neff, ² M. Montalbano, ¹ N. Ozden*, ² H. Muslu, ² Y.M. Lee, ² G. Slapak, ¹ K. Safdar, ¹ R. Morrero, ² J. Nery, ¹ D. Weppeler, ¹

Introduction: Recurrent HCV in the liver recipients is a major concern. We present our preliminary data using pegylated alpha-2b interferon and ribavirin in naïve HCV-R patients.

Methods: Treatment: pegylated alpha-2b interferon (1.5mcg/kg) and ribavirin (400-600mg/d) therapy for at least 24 weeks. Side effects recorded: neutropenia (<750 cells), anemia (hemoglobin <8grams), thrombocytopenia and depression. Definition of HCV-R: increase in liver chemistries, histopathologic findings with inflammation along with COBAS AMPLICOR[®] Hepatitis C virus Test, version 2.0 (HCV RNA Qualitative PCR) and COBAS AMPLICOR[®] HCV MONITOR TEST-version 2.0 (HCV RNA quantitative PCR) assays. Immunosuppression: tacrolimus with steroid tapering by week 12-20.

Results: Thirty OLT recipients were included in the study. Mean age was 54yrs, mean time from OLT was 29.2 months, Hispanics (57%) Caucasians (40%) and African Americans (3%). Eight out of 30 patients (27%) became HCV non detectable. The following dose adjustments were required: PEG-IFN was reduced in 12 out of 30 (40%) and 13 out of 30 patients had (43%) to decrease in ribavirin dosage. Therapeutic interventions were: 3/30 (10%) received blood transfusions, 6/30 (20%) received erythropoietin and 13/30 (43%) had to receive neupogen. Clinical depression with medical therapy was seen in 13/30 (43%).

Conclusion: Combination PEG-IFN with ribavirin appears to effective therapy in HCV-R. The frequency of side effects necessitating cessation of treatment was greater than generally reported in the non-transplant setting. This data, although preliminary, reveals the difficulty and caution that must be considered when treating HCV-R liver transplant recipients with combination pegylated interferon and ribavirin therapy.

PRELIMINARY TREATMENT RESULTS OF PEGYLATED INTERFERON ALPHA 2B AND RIBAVIRIN IN LIVER TRANSPLANT RECIPIENTS WITH RECURRENT HEPATITIS C VIRUS NONRESPONSIVE TO INTERFERON ALPHA2B AND RIBAVIRIN

G.W. Neff, ² M. Montalbano, ¹ N. Ozden*, ² H. Muslu, ² Y.M. Lee, ² K. Safdar, ¹ R. Morrero, ² J. Nery, ¹ D. Wepler, ¹ J. Madariaga, ¹

D. Levi, ¹ S. Nashida, ¹ T. Kato, ¹ E. Schiff, ² A. Tzakis, ¹

**Presenting Author, ¹University Of Miami Liver/GI/Transplantation, Miami, FL, USA ²University of Miami Hepatology, Miami, FL, USA*

Introduction: Recurrent HCV in the liver recipients is a major concern. We present data from a prospective trial of pegylated interferon and ribavirin combination treatment in recurrent HCV nonresponder (HCV-NR).

Methods: Treatment: pegylated interferon-2b (1.5 mcg/kg/wk) and ribavirin (400-600 mg/d) therapy. Side effects recorded: anemia, neutropenia, thrombocytopenia and depression. T HCV-R was defined: increase in liver chemistries, histopathologic findings consistent with inflammation along with viral recurrence and HCV viremia. HCV RNA serology was done using COBAS AMPLICOR[®] Hepatitis C virus Test, version 2.0 (HCV RNA Qualitative PCR) and COBAS AMPLICOR[®] HCV MONITOR TEST-version 2.0 (HCV RNA quantitative PCR) assays.

Results: Thirty-two OLT patients were given combination treatment. 8 Hispanics (25%), 24 Caucasians (75%). Mean time from transplant (24.2 mos) and Mean age was 53.1yrs. Biochemical improvements was seen in 16/32 (50%) and 6/32 (18%) became HCV nondetectable. Side effects included; clinical depression 16/32 (50%), neutropenia 14/32 (43%), reduced pegylated interferon dosing 19/32 (60%), reduced ribavirin 9/32 (28%) and blood transfusions related to ribavirin 2/32 (6%). Combination therapy had to be discontinued secondary to drug intolerance in 9 out of 32 patients (28%).

Conclusion: Although treatment of HCV-NR with combination pegylated alpha-2b interferon and ribavirin was beneficial in 18% of patients, several transplant recipients suffered from depression, neutropenia, thrombocytopenia or anemia. Safety data that we obtained from this study has prompted us to start HCV liver transplant recipients with lower doses of pegylated interferon-2b and ribavirin and increase in escalating dosages if tolerated by the recipient.

PILOT STUDY OF TREATMENT WITH PEGYLATED INTERFERON AND RIBAVIRIN IN LIVER TRANSPLANT RECIPIENTS WITH HEPATITIS C INFECTION

B. Roche, ¹ A.M. Roque-Afonso, ³ M. Sebah, ² C. Feray, ¹ C. Guettier, ² E. Dussaix, ³ D. Castaing, ¹ D. Samuel*, ¹

*Presenting Author, ¹Centre Hepato-Biliaire, ²Department Of Pathology, ³Department Of Microbiology, Hospital P.Brousse, Villejuif, France

BACKGROUND: Combination of peg-interferon and ribavirin is the most effective treatment of hepatitis C (HCV) for immunocompetent patients. Efficacy and safety of this treatment is unknown in liver transplant (LT) recipients.

METHODS: 22 liver transplant patients (13 M, 9 F, mean age: 58 years) with histological evidence of HCV infection were treated with pegylated interferon a-2b (mean dose 1 mg/kg/week) ribavirin (mean dose 7.5 mg/kg/day) combination at a mean of 95.5 months (2-175) after LT. The planned duration of treatment was 6 months in non-1 genotype (n=5) and 1 year in genotype 1 (n=17). Six patients were non responders and 1 relapser to a previous treatment with interferon a-2b and ribavirin. Serum HCV RNA was measured every 12 weeks up to 24 weeks following completion of therapy.

RESULTS: Normalization of ALT was observed in 10/22 (45%), negativization of HCV RNA in 12/22 (54%) during treatment, 11/22 (50%) at the end of therapy and 4/22 (18%) 6 months following completion of therapy. Sustained virologic response was 11% in genotype 1 and 40% in genotype non-1, 26% in naive patients and 0% in previously treated patients. In 2 patients HCV RNA negative at 12 months, treatment was continued. The following dose adjustments were required: 6/22 (27%) decrease in peg interferon (neutropenia n=2, clinical depression n=4), 10/22 (45%) decrease in ribavirin therapy due to anemia. Therapy was discontinued in 14/22 (63%) patients: 8/22 (36%) due to lack of response and 6/22 (27%) related to drug intolerance (i.e. rejection n=3, acute pancreatitis n=1, depression n=1, death n=1).

CONCLUSION: Sustained virologic response using pegylated interferon a-2b and ribavirin combination was observed in 20% of LT patients with HCV infection. The high rate of drug intolerance and lower response rates observed as compared to those in the immunocompetent population were limiting factors in the transplant setting.

PREDICTORS OF VIROLOGIC RESPONSE IN COMBINATION THERAPY WITH INTERFERON (IFN) ALFA 2B PLUS RIBAVIRIN OF RECURRENT HEPATITIS C AFTER LIVER TRANSPLANTATION (LT)

B. Lavezzo*, ¹ A. Franchello, ² A. Smedile, ¹ D. Cocchis, ² E. David, ³ A. Barbui, ⁴ A. Ottobrelli, ¹ M. Fadda, ⁵ A. Brunati, ² M. Salizzoni, ²
M. Rizzetto, ¹

*Presenting Author, ¹Dept Of Gastroenterology, ²Dept Of Liver Transplant Surgery, ³Dept Of Pathology Division, ⁴Dept Of Virology Division, ⁵Dept Of Clinical Nutrition Service, Molinette Hospital, Turin, Italy

Background: combination treatment (CT) with IFN plus ribavirin is efficacious in small group of patients (pts) with recurrent hepatitis C after LT. Predictor factors of response are lacking.

Aim: to evaluate pre-treatment predictors of virologic response (negative HCV-RNA by PCR, Monitor Roche) at end of treatment (ETVR) and at 6 months (mo) of follow-up (SVR) in pts treated with CT for recurrent hepatitis C.

Methods: we evaluated 108 pts, mean age 53 yr (29-65), 77% males 76% genotype 1, with recurrent hepatitis C after LT, histology at baseline: 20 pts acute hepatitis, 88 pts chronic hepatitis with mean grading score of 5/18 (4-11) and mean staging score 2/6 (1-5). They were treated with IFN alfa 2b 3 MU x 3 weekly plus ribavirin 800 mg/die for 6 or 12 mo. Median time LT to treatment was 10 mo (2-86) Immunosuppressive therapy was cyclosporine in 63%, FK in 37% of pts. Mean ALT levels pre-treatment was 238 UI/L (50-1000), mean HCV-RNA level 38 MEq/ml (0, 7-120). Age, gender, immunosuppression, baseline ALT and HCV-RNA levels, histological grading and staging pre-treatment duration of therapy, time interval from LT to start of therapy, genotype were evaluated by linear multivariate regression analysis.

Results: ETVR was obtained in 29, 6% of pts, SVR in 23%. HCV genotype non-1 responded better than genotype 1 (SVR 46% vs 16%, p: 0, 001). Age and baseline HCV-RNA were predictors of ETVR (p < 0.05), but not SVR (age p: 0, 07). Duration of therapy was correlated with SVR, but virologic relapse occurred only in genotype-1 pts. In relapsed pts serum HCV-RNA became negative just before the end of therapy.

Conclusions: in LT genotype non-1 is predictor of SVR. In genotype-1 duration of therapy should be personalized to obtain a better and stable efficacy of treatment.

DOES INTERFERON TREATMENT OF CHRONIC HEPATITIS C AFFECT THE LONG TERM CLINICAL COURSE AFTER RENAL TRANSPLANTATION?

G.E. Shiha*, ¹ M.A. Sobh, ² I.M. Hassan, ² A.F. Elhabashi, ²

* Presenting Author, ¹ Internal Medicine Dept Elmansoura University, Almansoura, Egypt ² Nephrology Centre Elmansoura University, Almansora, Egypt

Background: Liver disease is an important cause of morbidity and mortality after renal transplantation.. This work is a trial to show whether antiviral treatment should be given to haemodialyzed patients with chronic HCV who are candidates for kidney transplantation and to evaluate their long term clinical course after renal transplantation.

Methods: 50 patients with biopsy proven chronic hepatitis C and positive HCV-RNA were prospectively assigned into 2 groups: 18 patients received INF μ 2b therapy (3MU 3 times weekly) for 24 weeks and 32 patients who received no antiviral and was assigned as a control group.

Results: The 2 groups were demographically similar and had similar Knodell scores. IFN μ 2b was discontinued in 2 patients (11%) due to persistent leucopenia. Mean serum ALT decreased to normal values in all patients of the IFN group. HCV RNA turned negative in 10 patients (55%) of the treatment group and in none of the control. All patients received living related kidney transplants and followed up for almost 4 years. Transaminases remained normal in all patients of the IFN group after transplantation. 2 patients had a virological relapse. Chronic allograft nephropathy (CAN) developed in 13 (40.6%) of the control group and in 1 (5.6%) of the IFN group (p < 0.009). 8 patients (25%) of the control group and one patient of IFN group (5.6%) developed chronic graft failure (p < 0.08).

Conclusion: Patients treated with INF μ 2b enjoyed better liver function with lower chronic graft dysfunction. We therefore recommend treating HCV patients before renal transplantation.