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TREATMENT WITH PEG-INTERFERON ALFA-2B (PEG-IFN) PLUS RIBAVIRIN COMPARED TO INTERFERON ALFA-2B (INF ALFA-2B)PLUS RIBAVIRIN ON SUBJECTS WITH CHRONIC HEPATITIS C INFECTED WITH HCV GENOTYPE 4. Gamal Esmat, A M Abouzied, Fatma Abdel-Aziz, M K Mohamed, Mohamed Abdel-Hamid, M S El Raziky, S A Ismail, K R Zalata, N N Mikhail, Tropical Medicine Institute, Cairo, Egypt; Alan Fix, Thomas Strickland, University of Maryland, Baltimore, MD; Maria H Sjogren, Walter Reed Army Medical Center, Washington, DC

Egypt has a prevalence rate of infection with hepatitis C that varies between 9% and 24%; approximately 90% is genotype 4. There are limited data for small numbers of patients on the effect of interferon therapy on HCV genotype 4-chronic hepatitis (CHC) subjects. The objective of this study is to assess the antiviral response of Egyptian subjects with CHC to combined therapy of PEG-INF plus ribavirin or IFN alfa2-b plus ribavirin. A total of 172 previously untreated CHC subjects have been enrolled in the study; 138 (80%) are infected with HCV genotype 4. Patients were randomized to receive PEG-IFN 100 μg/week plus ribavirin 800-1000 mg based on body weight (< 70kg or > 70 kg) or 3 MU/TIW IFN alfa-2b plus ribavirin (similar dose). If, at 24 weeks, HCV RNA is undetectable treatment is continued for 48 weeks; otherwise the medications are stopped. Antiviral response is defined as undetectable HCV RNA, tested by qualitative nested RT-PCR. Both randomized groups are similar in baseline characteristics: mean age is 39.3 years; 132 are male (77%); mean body mass index is 27.9 kg/m2; 15% had high viral load; mean liver inflammatory score was 7/18 and fibrosis stage 2/6. Currently, 116 patients have completed 12 weeks, and 67 of them completed 24 weeks of therapy. At 12 weeks, HCV RNA was undetectable in 42/59 (71%) of the PEG-IFN group and in 37/57(65%) in the IFN alfa-2b group. At 24 weeks, HCV RNA was undetectable in 20/30 subjects (66%) in the PEG-IFN group and 22/37(59%) in the IFN alfa-2b group. In this ongoing trial, both PEG-IFN and IFN alfa2-b in combination with ribavirin appear to be effective in treating chronic hepatitis patients with HCV genotype 4. The preliminary results are encouraging, and antiviral therapy of HCV genotype 4-infected subjects appears to be warranted.

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OPTIMIZED VIROLOGICAL RESPONSE IN GENOTYPE 4 CHRONIC HEPATITIS C PATIENTS TREATED WITH PEGINTERFERON ALFA-2A (40KD) (PEGASYS®) IN COMBINATION WITH RIBAVIRIN (RBV). Moises Diago, General Universitario, Valencia, NJ, Spain; Stephanos J Hadziyannis, Henry Dunant Hospital, Athens, Greece; Henry Bodenheimer Jr, Beth Israel Medical Center, New York, NY; Tarek Hassanein, University of California, San Diego, CA; Sonia Uchman, Attleboro Gastroenterology, Attleboro, MA; Patrick Marcellin, Hopital Beaujon, Clichy, France; Giuliano Ramadori, Georg-August Universität, Göttingen, Germany; Jean Delwaide, Domeine Universitaire Du Sart Tilman, Liège, Belgium; Farhad Sedarati, Hoffmann-La Roche Inc, Nutley, NJ

Background: Patients with chronic hepatitis C (CHC) infected with HCV genotype 4 have traditionally been described as 'difficult-to-treat'. Recently, we showed that the poor sustained virological response (SVR) of these patients to therapy with standard interferon (SVR 0-5%; Zylberberg H et al. *Ann Intern Med.* 2000;135:845-846) can be overcome by treatment with peginterferon alfa-2a (40KD) alone (SVR 45%; Sherman M et al. *Ann Intern Med.* 2001;135:927-928) or in combination with RBV (SVR 77%; Rodes J et al. 8th International Symposium on Hepatitis C and Related Viruses 2001)
Objectives: To study the efficacy and safety of 24 or 48 weeks of treatment with peginterferon alfa-2a (40KD) combined with an 800 or 1000-1200 mg daily dose of ribavirin (RBV) and to determine an optimal treatment regimen in CHC patients infected with genotype 4.
Methods: A total of 49 CHC patients infected with HCV genotype 4 identified in 2 phase III studies (NV15801 and NV15942) were included in these analyses. Patients in the NV15801 trial (n = 13) were treated with peginterferon alfa-2a (40KD) 180 μg sc qw plus RBV 1000-1200 mg qd for 48 weeks. Patients in NV15942 trial (n = 36) were treated in one of 4 groups: peginterferon alfa-2a (40KD) 180 μg sc qw plus RBV 800 mg qd or RBV 1000-1200 mg qd for 24 weeks or 48 weeks based on body weight (<75 kg or ≥75 kg). Efficacy assessments consisted of HCV RNA (undetectable HCV RNA using COBAS AMPLICOR® HCV Test, v2.0, lower limit of sensitivity 50 IU/mL) and serum ALT assessments (reduction below the upper limit of normal range) at the end of a 24-week posttreatment follow-up period. Safety was assessed by evaluation of adverse events and laboratory tests.
Results: The majority of patients were from Europe (n=34) and the United States (n=13). Patients were predominantly male (69%) with baseline viral load ranging from 0.05 to 8.18 million copies/ml. (13 patients (26%) had a viral load >2 million copies/mL). Twelve patients (24%) had cirrhosis. Among patients treated with peginterferon alfa-2a (40KD) plus 1000-1200 mg RBV for 48 weeks in both studies, 19 (79%) achieved an SVR. Patients treated with RBV 800 mg for 48 weeks or RBV 1000-1200 mg for 24 weeks achieved lower SVRs of 63% and 67%, respectively. No SVR was achieved in patients treated with RBV 800 mg for 24 weeks. The majority of patients who were sustained virological responders were also sustained biochemical responders as measured by normalization of their serum ALT concentrations. The treatments were well tolerated and only 4 patients discontinued therapy for adverse events (n = 3) or laboratory abnormality, all in the group treated with RBV 1000-1200 mg dose for 48 weeks.
Conclusion: Our results indicate that both treatment duration and RBV dose affect treatment outcome and that the optimal treatment regimen in this patient population appears to be peginterferon alfa-2a (40KD) + 1000-1200 mg qd RBV given for 48 weeks. Although genotype 4 CHC patients, like those infected with genotype 1, need to be treated aggressively for optimal response, they seem to be able achieve SVRs similar to the very high SVR reported for patients with genotype 2/3 infection (Hadziyannis SJ et al. EASL 2002; Shiffman ML et al. AASLD 2002). Therefore, it may no longer be appropriate to categorize infection with HCV genotype 4 as a 'difficult-to-treat' disease.

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PROSPECTIVE EVALUATION OF EARLY VIROLOGICAL RESPONSE ASSOCIATED WITH PEGINTERFERON ALFA-2A (40KD) (PEGASYS®) AND RIBAVIRIN FROM A PHASE IV, RANDOMIZED STUDY EXAMINING THE EFFECTS OF TREATMENT DURATION IN HEPATITIS C PATIENTS INFECTED WITH GENOTYPE 1. C E Brandao, Graffée e Guinle Hospital, Gaffrée, Brazil; R Perez-Gomez, Civil Hospital of Guadalajara, Guadalajara, Mexico; M G Pessoa, Emilio Ribas Infectious Disease Hospital, Sao Paolo, Brazil; M A Olivera-Martinez, National Institute of Medical Sciences and Nutrition, Mexico City, Mexico; C Caramori, UNESP-Botucatu, Botucatu, Brazil; C V Bazan-Perez, Tijuana General Hospital, Tijuana, Mexico; M Patelli, PUCAMP, Sao Paolo, Brazil; R Torres-Ibarra, Infectious Disease Hospital, Guadalajara, Mexico; A Barone, University of Sao Paulo, Sao Paolo, Brazil; M Dehesa-Violante, National Medical Centre, Mexico City, Mexico; F Carrilho, University of Sao Paulo, Sao Paolo, Mexico; R Vivar, Roche Mexico, Mexico City, Mexico; F Tatsch, Hoffmann-La Roche Ltd, Sao Paolo, Brazil

Background: Analyses of data from a large phase III study have shown that combination therapy with peginterferon alfa-2a (40KD) and ribavirin (RBV) results in a significant improvement in sustained virological response (SVR) compared with the combination of standard interferon and ribavirin. This study further showed that early virological response (EVR), defined as loss of serum HCV RNA or 2-$\log_{10}$ decrease from baseline HCV RNA by week 12, was a strong predictor of SVR (86% of patients achieved EVR, with 65% going on to SVR). Importantly, 80% adherence to study medication in EVR patients further improved SVR to 75%. (Fried MW et al. *Gastroenterology.* 2001;120 (5 suppl 1):A55).
Objective: To prospectively evaluate early virological response in an ongoing, randomized, phase IV study comparing the efficacy and safety of two treatment durations with peginterferon alfa-2a (40KD) and ribavirin in patients infected with genotype 1.
Methods: A total of 220 naive patients with histologically proven hepatitis C, who are HCV RNA positive and have abnormal ALT will be randomized to receive peginterferon alfa-2a (40KD) 180 μg once weekly and ribavirin (RBV) 800 mg daily for either 24 or 48 weeks. Patients with genotypes 2 and 3 will be treated in an observation arm for 24 weeks. All patients will be followed for an additional 24-week treatment-free period. Efficacy assessments consist of HCV RNA (COBAS AMPLICOR® HCV Test, v2.0, sensitivity of 50 IU/mL and AMPLICOR MONITOR® Test, v2.0, sensitivity 600 IU/mL) at weeks 4, 12, 24, 36 and 48 of the treatment period and at weeks 12 and 24 of the treatment-free period. Safety assessments consist of clinical and laboratory evaluations.
Results: To date, 176 patients have been randomized and 115 have completed 12 weeks of treatment. The baseline characteristics of the patients were as follows: 66% male, 58% Caucasian, mean age of 41 years and mean body weight of 76 kg. Viral load was >0.8 X 10^6 IU/ml. in 57% of the patients. The proportion of treated patients achieving an EVR at week 12 is summarized below.
Conclusion: These interim data confirm the previously reported marked association between EVR and peginterferon alfa-2a (40KD) plus RBV therapy, even in patients with genotype 1 infection (Fried MW et al. *Gastroenterology.* 2001;120 (5 suppl 1):A55). The ability of these early responses to predict SVR will be evaluated.

	EVR* (Week 12) % (n)	Patients With EVR That Have Negative HCV RNA (Week 12) % (n)
Genotype 1 (n=67)	72% (48)	64% (31)
Genotype 2/3	94% (45)	95% (43)
All Patients (n=115)	81% (93)	80% (74)

*2-$\log_{10}$ decrease in HCV RNA or HCV RNA negative.

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DEVELOPMENT OF HEPATOCELLULAR CARCINOMA IN CHRONIC TYPE B LIVER DISEASES: A STUDY ON INFLUENCE OF FIBROSIS, INFLAMMATION AND HBV GENOTYPES. Hajime Sumi, Fumio Imazeki, Osamu Yokosuka, Tomoko Kurihara, Takaaki Imamura, Tatsuo Kanda, Kenichi Fukai, Hiromitsu Saisho, Department of Medicine and Clinical Oncology, Graduate School of Medicine, Chiba University, Chiba, Japan

Background: Epidemiological studies have demonstrated a strong relationship between hepatocellular carcinoma (HCC) and chronic hepatitis B virus (HBV) infection. Several factors such as cirrhosis are reported to play roles in hepatocarcinogenesis. The importance of liver inflammation in the development of HCC was demonstrated in a mouse model with liver inflammation. HBV genotype also suggested to be correlated with the clinical features of HBV infection. On the other hand, recent molecular biological studies have revealed the oncogenic potential of the HBV virus itself, suggesting that the mere infection of HBV may be a risk factor for the development of HCC. **Aim:** This study was performed to elucidate the roles of hepatic inflammation, existence of cirrhosis and HBV genotype in the development of HCC. **Methods:** The subjects were 332 consecutive patients with chronic HBV infection who were followed for at least 2 years at the First Department of Internal Medicine, Chiba University Hospital. Liver function tests were performed at least every 3 months and ultrasonography was performed every 6-12 months. Patients whose serum alanine aminotransferase (ALT) level remained within the normal range during at least the last 2 years of follow-up were defined as having a sustained normal ALT level. The diagnosis of cirrhosis was made based on either the finding of cirrhosis on biopsy, or the presence of the typical ultrasonographic findings suggestive of cirrhosis and evidence of portal hypertension. The HBV genotype was determined using the patients' sera with commercial kit (Tokushu-Meneki Laboratory, Tokyo, Japan). The diagnosis of HCC was made by liver biopsy or imaging studies. **Results:** Of the 332 patients in this study (207 (62.3%) men and 125 (37.7%) women, with a mean age of 36.0 ± 13.2), 43 (12.9%) had cirrhosis and 289 (87.1%) had chronic hepatitis without cirrhosis. The distribution of HBV genotypes was A in 7 (2.1%), B in 40 (12.0%) and C in 285 (85.9%) patients. None of the patients had genotype D, E, or F. Sustained normalization of the ALT level during the last 2 years of follow-up was observed in 121 patients (36.4%). During a mean follow-up period of 8.6 ± 5.0 (S.D.) years, HCC developed in 34 cases (10.2%). HCC developed in 23 (8.0%) of the 289 originally non-cirrhotic patients with a yearly incidence of 1.0% and in 11 (25.6%) of the 43 cirrhotic patients with a yearly incidence of 2.9% ($p<0.001$). HCC developed in 6/121 (5.0%) patients with sustained ALT normalization and in 27/211 (12.8%) without sustained ALT normalization ($p<0.022$). With regard to HBV genotype, 4 (10.0%) of 40 patients with genotype B and 30 (10.5%) of 285 patients with genotype C developed HCC (p: not significant), with a yearly incidence of 1.1% and 1.2%, respectively. None of the 7 patients with genotype A developed HCC. Of the 34 patients who developed HCC, 14 (41.1%) had a non-cirrhotic liver and 20 (58.9%) had a cirrhotic liver at the time of developing HCC. 3 (14.6%) of the 34 patients with HCC had both a sustained normal ALT level and a non-cirrhotic liver when HCC was found. **Conclusions:** A significant proportion of the HCC cases had developed in non-cirrhotic patients with sustained ALT normalization, suggesting the strong carcinogenic potential of HBV itself. The HBV genotype seems to have limited influence on the development of HCC, while liver cirrhosis and inflammation as manifested by the serum ALT level were additional risk factors for the development of HCC.