

## **Publications du service d'Hépatologie Adultes (1999-2009 ; 2011)**

**2011**

**SHIFFMAN M.L., POL S., ROSTAING L., SCHIFF E., THABUT D., ZEUZEM S., ZONG J., FREDERICK D., ROUSSEAU F.**

Efficacy and pharmacokinetics of adefovir dipivoxil liquid suspension in patients with chronic hepatitis B and renal impairment.

*J. Clin. Pharmacol.*, 51 (9), 1293-1301, 2011

(Services cités : Hépatologie Adulte)

The study evaluated whether a liquid suspension of adefovir dipivoxil (ADV) is effective and safe when dose adjusted based on varying degrees of renal impairment in patients with chronic hepatitis B. Patients had stable mild, moderate, or severe renal impairment or end-stage renal disease. Twenty-eight patients were enrolled: 10 (mild), 12 (moderate), and 6 severe renal impairment or end-stage renal disease with hemodialysis. Statistical testing demonstrated that daily dosages of ADV liquid suspension at 10 mg and 5 mg in the mild and moderate renal impairment groups, respectively, were clinically similar to ADV 10-mg tablets. However, the antiviral effect observed with the 5-mg/d dose was clearly numerically less than that observed with the 10-mg/d dose. Steady-state adefovir plasma exposures after administration of the ADV liquid suspension were generally within the ranges observed in patients with normal renal function. Treatment with ADV liquid suspension for up to 48 weeks was generally well tolerated. The daily dose-adjustment approach was not clearly safer or more efficacious than the dosing-interval adjustment. Therefore, the results do not support daily ADV dosing using a liquid suspension over the current strategy of adjustment of the ADV dosing interval in patients with impaired renal function.

**2008**

**GHOSN J., THIBAUT V., DELAUGERRE C., FONTAINE H., LORTHOLARY O., ROUZIOUX C., POL S., CHAIX M.L.**

Sexually transmitted hepatitis C virus superinfection in HIV/hepatitis C virus co-infected men who have sex with men.

*AIDS*, 22 (5), 658-661, 2008 ; (Facteur d'Impact 2007 : **5,842**)

(Services cités : Infectiologie, Laboratoire de Microbiologie, Hépatologie Adulte)

We report two cases of sexually transmitted hepatitis C virus (HCV) superinfection in HIV/HCV-co-infected patients with high-risk sexual behaviour. The two patients had chronic HCV and a history of sexually transmitted infections. HCV superinfection was confirmed by phylogenetic analysis. No risk factors for HCV were found except unprotected anal sex with multiple casual male partners. HCV serology and serum HCV RNA should be examined periodically in HIV-infected men who have sex with men engaging in high-risk sexual behaviours.

**CHOSSEGROS P., MELIN P., HEZODE C., BOURLIERE M., POL S., FHIMA A., FILOCHE B., TREPO C., COUZIGOU P., OUZAN D., GAGNON A.**

A French prospective observational study of the treatment of chronic hepatitis C in drug abusers.

*Gastroentérol. Clin. Biol.*, 32 (10), 850-857, 2008 ; (Facteur d'Impact 2007 : **0,846**)

(Services cités : Hépatologie Adulte)

The objective of this prospective, multicenter, observational study was to evaluate healthcare for hepatitis C virus (HCV)-infected drug abusers in France and to determine predictors of successful therapeutic intervention. A total of 170 drug users were recruited from 40 French centers. Three centers recruited 66 participants (38.8%), and one to eight patients each were enrolled from 37 other centers (n=104). A sustained viral response (SVR) was seen in 65 (38.2%) patients. SVR rates were significantly higher in compliant than in non-compliant patients (43.5% versus 23.9%;  $P=0.019$ ), in patients from high- rather than low-recruiting centers (54.5% versus 27.9%;  $P<0.001$ ) and in patients receiving Buprenorphine((R)) rather than methadone (48.1% versus 21.8%;  $P=0.001$ ). In patients, who completed both the treatment and follow-up (n=94), SVR rate was 57.4%. Buprenorphine((R)) substitution therapy and genotypes 2 or 3 HCV infection were associated with significantly higher rates of SVR ( $P<0.01$ , for both comparisons). In conclusion, successful care of hepatitis requires an active treatment policy of every center toward drug addicts. Additional studies are needed to explore the difference in SVR with methadone versus Buprenorphine((R)) therapy.

**2007**

**CADRANEL J.F., BOUJENAH J.L., BOURLIERE M., FONTANGES T., POL S., TREPO C., OUZAN D.**

Satisfaction of patients treated for chronic hepatitis C with the peginterferon alfa-2b pen device: the VISA observational study.

*Gastroentérol. Clin. Biol.*, 31 (2), 180-184, 2007 ; (Facteur d'Impact 2006 : **0,749**)

(Services cités : Hépatologie Adulte)

**OBJECTIVES:** This observational study aimed at evaluating the satisfaction of patients with chronic hepatitis C using the peginterferon (peg-IFN) alfa-2b pen device. **METHODS:** Consecutive patients were included when prescribed the pen device. Self-administered questionnaires relating to the progress brought by the pen, convenience/comfort, and the mode and security of injection were completed after the first injection and at 12 weeks. **RESULTS:** Six hundred and forty eight patients aged 45.7 +/- 12.1 years completed the 1st questionnaire; 70% were naive for any hepatitis C treatment. Five hundred and twenty five (81%) patients completed the 2nd questionnaire. Adherence to the pen device was >or=80% in more than 80% of the patients. Most (85%) patients declared that the pen brought important progress compared to traditional syringes. Satisfaction was high after the 1st injection and further increased 12 weeks later, with ease of use scoring 7.7 then 8.0 (P=0.007, 10-point scale), and rapidity of use scoring 8.0 then 8.2 (P=0.008); less painful injection scoring 7.9 at both time points. The proportion of self-injectors (no intervention of a health professional) increased from 32% to 58% (P<0.0001). Reasons for self-injecting were: easier injection (58%), no product/syringe handling (50%/41%), and assurance of exact dosing (45%). **CONCLUSION:** Patients were satisfied with the peg-IFN alfa-2b pen device. The proportion of self-injectors doubled over 12 weeks. Good treatment adherence, which is mandatory for therapeutic success, is expected from use if this device.

**MALES S., GAD R.R., ESMAT G., ABOBAKR H., ANWAR M., REKACEWICZ C., EL HOSEINY M., ZALATA K., ABDEL HAMID M., BEDOSSA P., POL S., MOHAMED M.K., FONTANET A.**

Serum alpha-foetoprotein level predicts treatment outcome in chronic hepatitis C.

*Antivir. Ther.*, 12 (5), 797-803, 2007 ; (Facteur d'Impact 2006 : **4,982**)

(Services cités : Hépatologie Adulte, U807)

**OBJECTIVES:** To analyse the association between serum alpha-foetoprotein (AFP) levels and sustained virological response (SVR) in treated patients. **METHODS:** One-hundred patients with chronic hepatitis C were treated with pegylated interferon alpha-2a plus ribavirin for 48 weeks. The primary endpoint was SVR. Linear regression analysis was performed to identify clinical, biological, and histological factors affecting baseline AFP levels. The association between pretreatment serum AFP and SVR was assessed by multivariate logistic regression analysis. **RESULTS:** Of 100 patients, 95 were infected with genotype 4, one with genotype 1, and four with undetermined genotype. The median serum AFP level was 4.5 ng/ml and AFP values ranged from 1.2 to 49.8 ng/ml. In multivariate analysis, higher fibrosis stage and higher steatosis score were independently associated with higher serum AFP levels. SVR rate was 61.0% (61/100), and was lower for patients with AFP levels above rather than below the median value (40.8% versus 80.4%, respectively, P < 0.001). In multivariate analysis, including adjustment for age, gender,

body mass index, steatosis score, fibrosis stage, ALT level, haemoglobin level, clotting time, HCV RNA viral load, and treatment dose received, a baseline serum AFP level above the median value was associated with a lower SVR rate (OR [95% CI]=0.10 [0.03-0.42], P < 0.001). None of the seven patients with increased (above 15 ng/ml) pretreatment AFP achieved SVR.

**CONCLUSIONS:** In this study, higher baseline serum AFP levels independently predicted a lower SVR rate among patients with chronic hepatitis C. If confirmed with genotypes other than 4, these findings would suggest adding serum AFP to the list of factors predictive of treatment response.

**ROSENTHAL E., PIALOUX G., BERNARD N., PRADIER C., REY D., BENTATA M., MICHELET C., POL S., PERRONNE C., CACOUB P.**

Liver-related mortality in human-immunodeficiency-virus-infected patients between 1995 and 2003 in the French GERMIVIC Joint Study Group Network (MORTAVIC 2003 Study)\*.

*J. Viral Hepat.*, 14 (3), 183-188, 2007 ; (Facteur d'Impact 2006 : **3,290**)

(Services cités : Hépatologie Adulte)

The objective of the present study was to determine mortality because of end-stage liver disease (ESLD) in a nationwide population of HIV-infected patients, 7 years following the introduction of highly active antiretroviral therapy (HAART). All departments of internal medicine and infectious diseases from the GERMIVIC Study Group prospectively recorded all deaths in HIV-infected patients during 2003. Fifty-nine departments, following a total of 20 940 HIV-infected patients, participated in the study. Results were compared with those of previous surveys conducted using similar methodology in 1995, 1997 and 2001. Among 215 deaths observed during 2003, 101 (46.9%) were related to AIDS, 27 (12.6%) to ESLD and 87 (40.5%) to other causes. Mortality because of ESLD represented 23.7% of non-AIDS-related deaths. Patients dying from ESLD had chronic hepatitis because of hepatitis C virus (HCV) in 92.6% of cases and moderate (30-60 g) or high (>60 g) alcohol consumption (43.5% and 26.0%, respectively). In this population, deaths because of ESLD were 1.5% in 1995, 6.6% in 1997, 14.3% in 2001 and 12.6% in 2003. The prevalence of hepatocellular carcinoma as a cause of death remained high in 2003 but stable when compared with 2001 (25% vs 14.8%). Treatment of hepatitis C in patients who died from ESLD was more frequent in 2003 (44.4%) than in 2001 (26.3%). Seven years after the introduction of HAART, ESLD associated with HCV infections is a leading cause of mortality in HIV-infected patients, which did not increase between the years 2001 and 2003.

**ROULOT D., BOURCIER V., GRANDO V., DENY P., BAAZIA Y., FONTAINE H., BAILLY F., CASTERA L., de LEDINGHEN V., MARCELLIN P., POUPON R., BOURLIERE M., ZARSKI J.P., ROUDOT THORAVAL F.**

Epidemiological characteristics and response to peginterferon plus ribavirin treatment of hepatitis C virus genotype 4 infection.

*J. Viral Hepat.*, 14 (7), 460-467, 2007 ; (Facteur d'Impact 2006 : **3,290**)

(Services cités : Hépatologie Adulte)

Hepatitis C virus genotype 4 (HCV-4) infection is progressing in Europe, where epidemiology and sustained virological response (SVR) seem to be different than in the Middle East. We analysed epidemiological features and SVR rates in a retrospective study of 1532 HCV-4-infected patients, including 1056 patients infected in France, 227 immigrants infected in Egypt and 249 in sub-Saharan Africa. SVR rates were assessed in 242 naive patients of the 1532, who

received peginterferon plus ribavirin for 48 weeks. HCV subtype 4a or 4d was the most common among patients infected in France, where the predominant route of transmission was intravenous drug abuse. The 4a subtype was largely predominant (93%) among patients infected in Egypt, where transmission was mostly because of parenteral treatment for schistosomiasis. More than seven different subtypes and no predominant route of infection were found in patients infected in sub-Saharan Africa. Liver fibrosis was significantly less severe in patients infected in France and Africa than in patients infected in Egypt. SVR rates were higher in patients infected in Egypt, compared with those infected in France or Africa (54.9%, 40.3% and 32.4%, respectively,  $P < 0.05$ ). An overall better response was observed in patients infected with the 4a subtype. In multivariate analysis, two factors were associated independently with SVR: the Egyptian origin of transmission and the absence of severe fibrosis. In conclusion, the distribution of HCV-4 subtypes varies with the geographical origin of transmission and affects the SVR following antiviral treatment.

**SORIANO V., PUOTI M., SULKOWSKI M., CARGNEL A., BENHAMOU Y., PETERS M., MAUSS S., BRAU N., HATZAKIS A., POL S., ROCKSTROH J.**

Care of patients coinfecting with HIV and hepatitis C virus: 2007 updated recommendations from the HCV-HIV International Panel.

*AIDS*, 21 (9), 1073-1089, 2007 ; (Facteur d'Impact 2006 : **5,632**)

(Services cités : Hépatologie Adulte)

2006

**ABEL M., SENE D., POL S., BOURLIERE M., POYNARD T., CHARLOTTE F., CACOUB P., CAILLAT-ZUCMAN S.**

Intrahepatic virus-specific IL-10-producing CD8 T cells prevent liver damage during chronic hepatitis C virus infection.

*Hepatology*, 44 (6), 1607-1616, 2006

(Services cités : Hépatologie Adulte)

CD8 T cell killing of hepatitis C virus (HCV)-infected hepatocytes is thought to contribute to liver damage during chronic HCV infection, whereas the participation of HCV-nonspecific immune cells is unclear. To visualize the spatial relationship of HCV-specific CD8 T cells with parenchymal target cells, and to examine their local functional activity in relation to hepatocellular necrosis and fibrosis, we used HLA tetramers and confocal microscopy in biopsies from 23 HLA-A2 or HLA-B7 patients with chronic HCV infection. Intrahepatic tetramer+ (HCV-specific) CD8 T cells protected from hepatic necroinflammatory disease activity, independently of age, gender, viral load, and viral genotype. Indeed, tetramer+ cells were scattered in the liver within regions of weak fibrosis (low laminin expression) and low hepatocellular apoptosis (TUNEL method), and expressed IL-10 but not IFN $\gamma$ . By contrast, tetramer-negative CD8 T cells were associated with active necroinflammatory liver disease, colocalized with strong laminin expression and hepatocellular apoptosis, and expressed more frequently IFN $\gamma$  than IL-10. Overall, liver regions harboring HCV-specific CD8 T cells tended to be healthier than areas containing only inflammatory cells of undefined specificity. In conclusion, HCV-specific IL-10-producing CD8 T cells, although not cytotoxic and unable to control viral replication, can attenuate hepatocellular necrosis, liver fibrosis, and inflammation mediated by bystander T cells, and may thus represent antigen-induced regulatory CD8 T cells. Therapeutic modulation of the intrahepatic balance between specific and bystander CD8 T cells might be beneficial in patients with chronic hepatitis C.

**BESSON C., CANIONI D., LEPAGE E., POL S., MOREL P., LEDERLIN P., VAN HOOFF A., TILLY H., GAULARD P., COIFFIER B., GISSELBRECHT C., BROUSSE N., REYES F., HERMINE O.**

Characteristics and Outcome of Diffuse Large B-Cell Lymphoma in Hepatitis C Virus-Positive Patients in LNH 93 and LNH 98 Groupe d'Etude des Lymphomes de l'Adulte Programs.

*J. Clin. Oncol.*, 24 (6), 953-960, 2006

(Services cités : Anatomo-Pathologie, Hématologie Adulte, Hépatologie Adulte)

**PURPOSE** Epidemiologic studies show an association between hepatitis C virus (HCV) and B-cell non-Hodgkin's lymphoma (NHL). Treatment and outcome of patients with diffuse large-cell lymphoma (DLCL) and HCV infection are still a matter of debate. **PATIENTS AND METHODS** We studied the HCV-positive patients with B-cell DLCL included in the Groupe d'Etude des Lymphomes de l'Adulte (GELA) programs LNH 93 and LNH 98. They were compared with the other patients with DLCL included in these programs. HCV infection prevalence was 0.5% (26 of 5,586 patients). Results Histologic types of HCV-positive DLCL were more frequently transformed from low-grade lymphoma than DLCL in HCV-negative patients (32% v 6%, P

=.02). This is also supported by more frequent spleen involvement in HCV-positive patients (46% v 17%,  $P < .001$ ). HCV-positive patients had more frequently elevated lactate dehydrogenase levels than other patients (77% v 55%,  $P = .02$ ). Outcome of HCV-positive patients was poorer for overall survival ( $P = .02$ ) but not for event-free survival ( $P = .13$ ). After matching on age and prognosis factors, at 2 years of follow-up, the overall survival was 56% (95% CI, 33% to 76%) among HCV-positive patients, versus 80% (70% to 89%), and the event-free survival was 53% (33% to 72%) versus 74% (64% to 84%). The short-term hepatic toxicity of chemotherapy was strongly increased among HCV-positive patients. After exclusion of the two subjects with chronic hepatitis B virus infection, the overall proportion of subjects undergoing hepatic toxicity was 65% (15 of 23 patients). **CONCLUSION** HCV-positive patients with DLCL differ from other patients both at presentation and during chemotherapy. Specific protocols evaluating antiviral therapy should be designed for these patients.

**BONNY C., FONTAINE H., POYNARD T., HEZODES C., LARREY D., MARCELLIN P., BOUELIERE M., BRONOWICKI J.P., MERLE P., ZARSKI J.P., SAPEY T., GUILLEMARD C., UGHETTO S., HENQUELL S., NICOLAS C., ROCHE C., RANDL K., BOMMELAER G., ABERGEL A.**

Effectiveness of interferon plus ribavirin combination in the treatment of naive patients with hepatitis C virus type 5. A French multicentre retrospective study.

*Aliment. Pharmacol. Ther.*, 24 (4), 593-600, 2006

(Services cités : [Hépatologie Adulte](#))

**Aim** To assess the rate of sustained virological response in naive hepatitis C virus-type 5 patients treated by standard interferon or percutaneous endoscopic gastrostomy-interferon (peg-interferon) and ribavirin combination for 48 weeks. **Patients and Methods** A total of 87 hepatitis C virus patients were included from 12 centres in France; 28 patients received interferon plus ribavirin and 59 were treated with peg-interferon plus ribavirin. **Results** Baseline characteristics were: mean age 58 +/- 11 years, sex ratio 1, 66% had metavir fibrosis score  $\geq$  F2, 21% were cirrhotics and 53% had pretherapeutic viral load  $\geq$  800 000 IU/mL. Sustained virological response was achieved in 64% and 58% of hepatitis C virus-5 patients treated with interferon and peg-interferon, respectively (NS). In adherent patients, sustained virological response was obtained in 75% of patients. Sustained virological response in hepatitis C virus-5 patients (60%) was significantly higher than sustained virological response in hepatitis C virus-1 patients (37%) ( $P = 0.0499$ ) and not significantly different from sustained virological response in hepatitis C virus-2-3 patients (63%) ( $P = 0.8098$ ). **Conclusions** Combination therapy is effective in 60% of hepatitis C virus-5-infected patients. Sustained virological response seems better in hepatitis C virus-5 patients than in hepatitis C virus-1 patients, and is similar to that of hepatitis C virus-2-3 patients. More studies are needed to determine optimal duration of treatment in hepatitis C virus-5 patients.

**CACOUB P., ROSENTHAL E., HALFON P., SENE D., PERRONNE C., POL S.**

Treatment of hepatitis C virus and human immunodeficiency virus coinfection: from large trials to real life.

*J. Viral Hepat.*, 13 (10), 678-682, 2006

(Services cités : [Hépatologie Adulte](#))

To analyse the barriers for anti-hepatitis C virus (anti-HCV) treatment in human immunodeficiency virus (HIV)-HCV coinfecting patients, we surveyed 71 physicians specializing in infectious disease (39%), internal medicine (27%), HIV/AIDS information and care (17%),

haematology (10%) and hepatology (6%). A standard data collection form was used to identify patients observed in 7 days in November 2004. Three hundred and eighty patients with the following characteristics were included: male gender 71%; mean age 41.5 years; HIV diagnosed 12 years ago; routes of transmission via injection drug use (78%); undetectable HIV viral load (235/373, 63%) or <10 000 copies/mL (86/373, 23%). HCV RNA was positive in 325 of 369 (88%) patients; HCV genotype was 1 or 4 in 65% and liver biopsy had been carried out in 56%. There were several explanations for the nontreatment of HCV in 205 of the 380 (54%) patients, with 2.4 reasons per patient: anti-HCV treatment was deemed questionable (n = 109) because of minor hepatic lesions, alcohol consumption, or active drug use; no liver biopsy had been performed (n = 68); treatment was contraindicated (n = 62), mainly for psychiatric reasons; there was physician conviction of poor patient compliance (n = 62) and patient refusal (n = 33). Patients having received anti-HCV treatment (n = 91) compared with those who had never received any (n = 205) were more commonly of European origin, had better control of their HIV infection, were followed by a hepatologist more often, had a liver biopsy more often and had more commonly a high HCV viral load ( $P < 0.001$ ). In 'real life' in France in 2004, more than half of the HIV-HCV coinfecting patients have never received anti-HCV treatment. The main reasons are a treatment that may be deemed questionable (minimal hepatic lesions, alcohol, active drug use), a lack of available liver biopsy, a psychiatric contraindication and physician conviction of poor patient compliance.

**DE LEDINGHEN V., RATZIU V., CAUSSE X., LE BAIL B., CAPRON D., RENO C., PILETTE C., OULES V., GELSI E., OBERTI F., VALLET-PICHARD A., LE PROVOST N., CADRANEL J.F.**

Diagnostic and predictive factors of significant liver fibrosis and minimal lesions in patients with persistent unexplained elevated transaminases. A prospective multicenter study.

*J. Hepatol.*, 45 (4), 592-599, 2006

(Services cités : Hépatologie Adulte)

**BACKGROUND/AIMS:** In patients with unexplained elevated transaminases, prognosis of the liver disease and factors associated with increased risk of liver fibrosis and normal/subnormal liver are unknown. The aim of this prospective study was to identify diagnosis and clinical and biological factors associated with significant (bridging) fibrosis and minimal lesions of the liver in patients with persistent unexplained elevated ALT levels. **METHODS:** From July 2002 through October 2004, all consecutive asymptomatic patients with unexplained chronically elevated ALT levels were included. All patients had clinical, biological, ultrasonographic examination and a liver biopsy. **RESULTS:** 272 patients (60.3% males, mean age 46.4 years, BMI 26.7) were included. Pathological findings were: minimal lesions (18.7%), steatosis (26.8%), NASH (32.7%), and miscellaneous (21.7%). Significant fibrosis was found in 27.4% of cases, including 9 cases of cirrhosis. By multivariate analysis, independent predictors of significant fibrosis were tobacco use (OR 2.5, 95% CI 1.34-4.74  $p=0.04$ ), BMI>25 (2.49, 1.31-4.73  $p=0.005$ ) and diabetes (4.41, 1.73-11.29  $p=0.002$ ). Independent factors associated with minimal lesions were female gender (OR 3.4 95% CI 1.73-6.75  $p<0.0001$ ) and BMI<25 (3.55, 1.8-6.98,  $p<0.0001$ ). **CONCLUSIONS:** In patients with unexplained chronically elevated transaminases, significant fibrosis is statistically associated with tobacco use, BMI>25 and diabetes, and minimal lesions are significantly associated with female gender and BMI<25.

**HALFON P., BOURLIERE M., POL S., BENHAMOU Y., OUZAN D., ROTILY M., KHIRI H., RENO C., PENARANDA G., SAADOUN D., THIBAUT V., SERPAGGI J.,**

**VARASTET M., TAINTURIER M.H., POYNARD T., CACOUB P.**

Multicentre study of hepatitis B virus genotypes in France: correlation with liver fibrosis and hepatitis B e antigen status.

*J. Viral Hepat.*, 13 (5), 329-335, 2006

(Services cités : Hépatologie Adulte)

The clinical significance of hepatitis B virus (HBV) genotypes is still under debate. The aims of this study were to assess the distribution of HBV genotypes in France and to identify the associations between HBV genotypes and patient demographics, severity of liver disease and HBeAg status in patients referred to tertiary care centres. This was a French, multicentre, retrospective study on 262 patients with chronic HBV infection. HBV genotypes were determined using INNO-LiPA. Liver fibrosis damage was evaluated by histological analysis of biopsy samples. Patients were mainly male (74%), of Caucasian (65%), Asian (17%) or African (18%) ethnicity and 36% were HBeAg positive. All A-G genotypes were found, the most frequent being genotypes D (27%) and A (24%), followed by E (13%) and C (12%), and B (7%). Mixed genotypes were detected in 16% of the cases. Genotype A was associated with sexual contact ( $P < 0.001$ ) and genotype D with transfusion ( $P < 0.001$ ) and HBe antibody positivity ( $P = 0.03$ ). The distribution of HBV genotypes differed with regard to the ethnicity, and may reflect migration patterns. Genotypes A and D were the most frequent in France. Genotype A was associated with HBeAg positivity and genotype D with HBe antibody positivity. In our European patients, we find no clear association between a given HBV genotype and liver disease severity.

**LE GAL F., GAULT E., RIPAULT M.P., SERPAGGI J., TRINCHET J.C., GORDIEN E., DENY P.**

Eighth major clade for hepatitis delta virus.

*Emerg. Infect. Dis.*, 12 (9), 1447-1450, 2006

(Services cités : Hépatologie Adulte)

Hepatitis delta virus is the only representative of the Deltavirus genus, which consists of 7 differentiated major clades. In this study, an eighth Glade was identified from 3 distinct strains. Deltavirus genetic variability should be considered for diagnostic purposes. Clinical consequences of the diversity have yet to be evaluated.

**LOUPY A., ANGLICHEAU D., MAMZER-BRUNEEL M.F., MARTINEZ F., THERVET E., LEGENDRE C., SERPAGGI J., POL S.**

Mycophenolate Sodium-induced Hepatotoxicity: First Report.

*Transplantation*, 82 (4), 581, 2006

(Services cités : Hépatologie Adulte, Transplantation & Réanimation Adulte)

**MANCINI-BOURGINE M., FONTAINE H., BRECHOT C., POL S., MICHEL M.L.**

Immunogenicity of a hepatitis B DNA vaccine administered to chronic HBV carriers.

*Vaccine*, 24 (21), 4482-4489, 2006

(Services cités : Hépatologie Adulte, U807)

Hepatitis B virus (HBV) is the major pathogen of chronic hepatitis and liver disease worldwide. Despite the availability of effective vaccines against hepatitis B for many years, over 370 million people remain persistently infected with HBV. Viral persistence is thought to be related to poor HBV-specific T-cell responses. Based on clinical data, the development of efficient methods capable of inducing strong T-cell responses is an important and primary step toward the development of immunotherapeutics against chronic HBV infection. We designed a phase I

clinical trial in chronic HBV carriers to assess safety, tolerability and immunogenicity of a DNA vaccine expressing HBV small (S) and middle (preS2 +S) envelope proteins. After occurrence of lamivudine breakthrough, 10 HBeAg positive patients with chronic hepatitis B were followed longitudinally before, during and after DNA vaccine therapy. Immunizations were well tolerated and adverse physical events were mild and considered unrelated to the vaccine. Proliferative responses to hepatitis B surface antigen (HBsAg) were detected in two patients after DNA injections. Following three injections of vaccine, interferon (IFN)-gamma-producing T-cells specific for the preS2 or the S antigen were detectable in 50 and 100% of the patients, respectively. Each patient recognized at least one peptide within the envelope domain encoded by the vaccine. Anti-preS2 antibodies and seroconversion to anti-HBe were detected in two patients. This study shows evidences for the safety and immunological efficacy of HBV-DNA vaccination and demonstrates that DNA vaccination can restore or activate T-cell responses in chronic HBV carriers.

**PIVERT A., PAYAN C., MORAND P., FAFI-KREMER S., DESHAYES J., CARRAT F., POL S., CACOUB P., PERRONNE C., LUNEL F.**

Comparison of serum hepatitis C virus (HCV) RNA and core antigen levels in patients coinfecting with human immunodeficiency virus and HCV and treated with interferon plus ribavirin.

*J. Clin. Microbiol.*, 44 (2), 417-422, 2006

(Services cités : Hépatologie Adulte)

Trak-C (Ortho-Clinical Diagnostics) is an enzyme-linked immunosorbent assay-based method capable of quantifying hepatitis C virus (HCV) core antigen (CA) in serum and could be an alternative to molecular detection and quantification of HCV RNA. We have evaluated the Trak-C assay in comparison with an HCV RNA quantitative assay (Versant HCV v3.0; Bayer Diagnostics) in the follow-up of 348 treated, human immunodeficiency virus (HIV)/HCV-coinfecting patients included in the ANRS HC02 RIBAVIC trial. ANRS HC02 RIBAVIC is a therapeutic, multicenter, randomized protocol comparing the efficacy of alpha interferon 2b (IFN-alpha2b) (3 million units three times a week)-ribavirin (800 mg/day) to that of pegylated IFN-alpha2b (1.5 mug/kg of body weight/week)-ribavirin (800 mg/day) during 48 weeks of treatment of HIV/HCV-coinfecting patients naive to HCV treatment. Patients were assessed for virological analysis at day 0 and weeks 4, 12, 24, 48, and 72. Correlation of HCV RNA and HCV CA at the initiation of treatment was excellent ( $r = 0.92$ ). HCV RNA and CA kinetics were similar during follow-up of HCV treatment from day 0 to week 72 whatever the group of response and genotype. The positive and negative predictive values of response to the treatment at week 4 were 59 and 94%, respectively, for HCV RNA load reduction of  $>2$  log and 54 and 94%, respectively, for HCV CA below the threshold value (4.18 log(10) pg/ml. 10(4)). Trak-C, a new assay able to quantify CA in HIV/HCV-coinfecting patients, correlates well with quantitative HCV RNA assays and is cheaper and easier to perform than molecular technology. HCV CA could be a valuable alternative test for therapeutic follow-up of coinfecting patients treated with IFN plus ribavirin in developing countries.

**POL S., MALLET V.O.**

Improving anti-hepatitis C virus therapy.

*Expert Opin. Biol. Ther.*, 6 (9), 923-933, 2006

(Services cités : Hépatologie Adulte)

The estimated prevalence of hepatitis C virus (HCV) infection is 2%, representing 123 million infected individuals worldwide. HCV infection burdens public health in relation to hepatic

(cirrhosis and its complications in 20% of patients) and extrahepatic (vasculitis) complications, and lessens quality of life. Major progress has been made in the last two decades for the diagnosis and treatment of HCV, including more appropriate screening strategies for HCV infection (improved sensitivity of serological and virological tests); a better evaluation of the impact of chronic HCV infection on the liver (semi-quantitative scoring systems of necro-inflammation and fibrosis on liver biopsy, non-invasive evaluation of fibrosis with biochemical markers and elastometry); and improved therapeutic regimens. This progress provides a better definition of who to treat (clinical impact or significant fibrosis); how to treat; tailoring therapies for doses and durations of the pegylated interferon plus ribavirin combination according to virological (mainly genotype and early viral kinetics, but also baseline viral load) and hosts factors (fibrosis, immune status, weight); and how to monitor efficacy and tolerance of therapy. The progress has now resulted in a 50% rate of complete HCV eradication, ranging 45 - 90% according to the genotype and especially in those patients with early viral response. New therapies, specifically HCV protease or polymerase inhibitors, in combination with pegylated interferon, or more potent and less toxic new formulations of interferons or ribavirin, will increase these encouraging results in the future.

#### **POL S.**

Impact of resistance to analogue antivirals and therapeutic strategies in situations of dialysis, kidney transplantation, vasculitis, and preemptive treatments in immunosuppressed patients.

*Gastroentérol. Clin. Biol.*, 30 (10 Pt 2), 31-33, 2006

(Services cités : Hépatologie Adulte, U807)

#### **POL S.**

Natural history of hepatitis B infection.

*Presse Médicale*, 35 (2 Pt 2), 308-316, 2006

(Services cités : Hépatologie Adulte, U807)

Hepatitis B virus (HBV) is transmitted by parenteral, sexual and perinatal routes. While fulminant hepatitis may occur in 1% of cases of symptomatic acute hepatitis, the principal problem of HBV infection is that it may become chronic, classically defined by carriage of HB surface antigens (HBsAg) for more than 6 months. This occurs in only 0.5 to 3% of immunocompetent adults but more frequently in children (up to 90%) and in immunocompromised patients (30 to 100%). The course of chronic HBV infection is characterized by variations in viral replication with spontaneous reactivation or discontinuation, and potential exacerbations observed clinically or by laboratory testing. The pathogenesis of HBV infection is mainly immune-mediated, resulting from host-virus interactions but also from the complexity of the virus itself (integration, mutation, occult replication). These factors explain the variety of presentations of chronic HBV infection, which range from immune tolerance to inactive carriage of HBsAg, passing through a stage of immune clearance, where chronic active hepatitis which may lead to cirrhosis (yearly incidence of 1.3 to 5.9%). Cirrhosis may be complicated by portal hypertension, liver failure, or hepatocellular carcinoma, which together explain 80% of the morbidity and mortality associated with HBV. The 5-year survival rate for HBV-related cirrhosis ranges from 52 to 82%. Immunosuppression, hepatitis D virus superinfection, and chronic alcohol consumption are the principal factors that modify this natural history. Chronic HBV infection is a major public health problem, particularly in developing countries, and it requires that efforts to make HBV vaccination universal be intensified.

**SERPAGGI J., CHAIX M.L., BATISSE D., DUPONT C., VALLET-PICHARD A., FONTAINE H., VIARD J.P., PIKETTY C., ROUVEIX E., ROUZIUX C., WEISS L., POL S.**

Sexually transmitted acute infection with a clustered genotype 4 hepatitis C virus in HIV-1-infected men and inefficacy of early antiviral therapy.

*AIDS*, 20 (2), 233-240, 2006

(Services cités : Hépatologie Adulte, Infectiologie, Laboratoire de Microbiologie, U807)

Background: Recent studies have suggested an increased risk of acute hepatitis C (HCV) infection in homosexual HIV-infected men and that early treatment with standard or pegylated interferon-alfa, alone or associated with ribavirin, significantly reduces the risk of chronic evolution in HIV-infected patients. Methods: A retrospective analysis of 12 HIV-infected patients who were consecutively diagnosed as developing acute HCV infection, defined by both seroconversion of anti-HCV antibodies and detection of serum HCV RNA in those with previous negative results. Ten of these patients received early antiviral treatment with standard or pegylated interferon-alfa, alone or associated with ribavirin. Results: The only risk factor in these patients was unprotected sexual intercourse with men. Acute HCV infection was asymptomatic in 10 patients, and the HCV genotype was 4d in 10 patients. The 10 genotype 4d viruses formed a monophylogenetic group and clustered separately from other local sequences of HCV genotype 4d, suggesting a common source of infection. None of the 10 patients who were treated early with antiviral therapy had a sustained virological response, as defined by undetectable HCV RNA 6 months after therapy. Conclusions: There is a risk of sexual transmission of HCV in HIV-infected men who have sex with men; the cluster of HCV genotype 4d suggested a common Source of infection and a failure in prevention counselling. Early treatment with standard interferon-alfa failed to prevent chronic evolution of HCV infection in this particular group of HIV-infected patients who had acquired this peculiar cluster of genotype 4 strains. (C) 2006 Lippincott Williams & Wilkins.

**SERPAGGI J., CARNOT F., NALPAS B., CANIONI D., GUECHOT J., LEBRAY P., VALLET-PICHARD A., FONTAINE H., BEDOSSA P., POL S.**

Direct and indirect evidence for the reversibility of cirrhosis.

*Hum. Pathol.*, 37 (12), 1519-1526, 2006

(Services cités : Hépatologie Adulte, U807)

The aim of this study was to assess the reversibility of cirrhosis after therapy in a large series of patients with cirrhosis from various etiologies. We performed a retrospective study of 113 patients with biopsy-proven cirrhosis who underwent specific therapy and follow-up biopsies. Two pathologists performed blinded analyses of indirect biochemical and morphological signs of cirrhosis. Fourteen (12.4%) of the 113 cirrhotic patients had biopsy-proven disappearance of cirrhosis, defined as a decrease of 2 or greater in their METAVIR fibrosis score: 8 were related to hepatitis C virus, 3 to hepatitis B virus, and 3 to autoimmune cirrhosis. Necro-inflammatory activity decreased from 2.4 +/- 0.65 to 0.85 +/- 0.9 (P =.004), and fibrosis from 4 to 1.7 +/- 0.61 (P =.001). Prothrombin time (n = 1), platelet count (n = 2), serum albumin level (n = 2), and ultrasound abnormalities (n = 6) normalized in patients who had initial abnormalities. Hyaluronic acid and procollagen type III serum level decreased in all. In the 11 patients with regression of viral cirrhosis, 2 were nonresponders and 9 were responders, including 2 relapsers. The 3 patients with regressive autoimmune cirrhosis were complete responders to immunosuppressive therapy. Using repeated liver biopsies, clinicobiochemical, radiologic, and endoscopic tests, we provide evidence for potential reversibility of cirrhosis after long-lasting suppression of the necro-

inflammatory activity of liver disease.

**VALLET-PICHARD A., MALLET V., POL S.**

FIB-4: A simple, inexpensive and accurate marker of fibrosis in HCV-infected patients.

*Hepatology*, 44 (3), 769, 2006

(Services cités : Hépatologie Adulte)

**VALLET-PICHARD A., POL S.**

Natural history and predictors of severity of chronic hepatitis C virus (HCV) and human immunodeficiency virus (HIV) co-infection.

*J. Hepatol.*, 44 (Suppl. 1), S28-S34, 2006

(Services cités : Hépatologie Adulte, U807)

Co-infection by the hepatitis C virus (HCV) is observed in up to 30% of HIV-infected individuals. In studies conducted in the 'pre-HAART era', the late consequences of HCV-related chronic liver disease were overshadowed by extra-hepatic causes of deaths, related to severe immune deficiency, and the impact of HCV infection on mortality of HIV-infected patients was low. While the development of HAART has resulted in a significant decrease in morbidity and mortality amongst HIV-infected patients, this clear benefit allowed the expression of liver-related complications associated with HCV chronic infection. The impact of HCV on HIV remains debated but HIV infection significantly modifies the natural history of HCV infection. HIV infection increases levels of HCV viraemia by 2- to 8-fold, resulting in a significant decrease in spontaneous recovery of acute hepatitis. HIV co-infection also worsens the histological course of HCV infection by increasing and accelerating the risk of cirrhosis or leading to rare but lethal fibrosing cholestatic hepatitis. Liver disease is now one of the leading causes of morbidity and mortality in co-infected patients, even if HAART and especially protease inhibitors, may decrease the severity of the liver disease and the liver-related mortality. Several non-exclusive pathogenic processes explain the increasing rate of liver complications associated with HCV-related liver disease.

**WOOTLA B., DASGUPTA S., MALLET V., KAZATCHKINE M.D., NAGARAJA V., FRIBOULET A., KAVERI S.V., LACROIX-DESMAZES S.**

Physiopathology of catalytic antibodies: the case for factor VIII-hydrolyzing immunoglobulin G.

*Blood Coagulat. Fibrinol.*, 17 (4), 229-234, 2006

(Services cités : Hépatologie Adulte)

Antibodies that are able to catalyze the antigen for which they are specific are produced spontaneously by the immune system. Catalytic immunoglobulins (Igs) both of the IgM and IgG isotypes have been detected in the serum of healthy donors, where they have been proposed to participate in the removal of metabolic waste and in the defense of the organism against invading pathogens. Conversely, antigen-specific hydrolytic IgG have been reported in a number of inflammatory, autoimmune and neoplastic disorders: their pathogenic effects have been demonstrated occasionally. The pathophysiological relevance of catalytic antibodies thus remains an elusive issue. Through the description of the pro-coagulation factor VIII as a model target antigen for catalytic antibodies, we propose that catalytic antibodies have either a beneficial or a deleterious role depending on the physiopathological context. Physiology thus relies on a delicate equilibrium between the levels of soluble target antigen and that of antigen-specific hydrolyzing immunoglobulins. Indeed, in patients with hemophilia A, in whom endogenous factor VIII is deficient or missing and exogenous factor VIII needs to be administered to treat hemorrhagic

events, the development of factor VIII-hydrolyzing IgG that inactivate the therapeutically administered factor VIII, may reveal deleterious. In contrast, in a situation in which excess factor VIII may be detrimental and lead to excessive coagulation, disseminated thrombosis and organ ischemia, as seen in severe sepsis, our recent data suggest that the presence of factor VIII-hydrolyzing IgG may be beneficial to the patient.

**YAZDANPANA H Y., de CARLI G., MIGUERES B., LOT F., CAMPINS M., COLOMBO C., THOMAS T., DEUFFIC-BURBAN S., PREVOT M.H., DOMART M., TARANTOLA A., ABITEBOUL D., DENY P., POL S., DESENCLOS J.C., PURO V., BOUVET E.**

Risk factors for hepatitis C virus transmission to health care workers after occupational exposure: A European case-control study.

*Rev. Épidémiol. Santé Publ.*, 54 (Sp.Iss. 1), S23-S31, 2006

(Services cités : Hépatologie Adulte, U807)

Background: Factors that influence the risk for HCV infection after occupational exposure to hepatitis C virus (HCV) have not yet been determined. The objective of this study was to assess potential risk factors for Hepatitis C seroconversion after occupational exposure to HCV. Methods: We conducted a European matched case-control study from 01/01/1991 through 31/12/2002. Cases were Health Care Workers (HCWs) who were HCV seronegative at the time of exposure, sustained a documented exposure to HCV, and present documented HCV seroconversion temporally associated with the exposure. Controls-HCWs had a documented exposure to HCV, were HCV seronegative at the time of exposure, and remained so at least 6 months later. Controls were matched to cases for the center and the time period of the exposure occurrence. Results: 60 cases and 204 controls were included. All cases were exposed to HCV-infected materials through percutaneous injuries. Those for whom information was available (61.6%) were exposed to viremic source patients. Multivariate conditional logistic regression analysis, in which HCV viral load was not introduced because of missing values, identified needle placed in the source patient's vein or artery (Odds Ratio [OR] = 100.1; 95% Confidence Interval [CI] = 7.3-1365.7), deep injury (OR = 155.2; 95% CI = 7.1-3417.2), and HCW's gender (M vs. F: OR=3.1; 95% CI = 1.0-10.0) as risk factors for HCV infection. In univariate unmatched analysis the risk of HCV transmission was increased H-fold (CI95% = 1.1-114.1) in HCWs exposed to sources with a viral load > 6 log(10) copies/mL when compared to sources with a HCV viral load < 4 log(10) copies/mL. Conclusion: The risk of HCV transmission after percutaneous exposure increases with a larger volume of blood, and, a higher titer of HCV in the source patient's blood. The role of HCW's gender need to be further investigated. The results of this study have important implications for counselling and follow-up of HCWs after exposure.

**2005**

**AARON L., LEBRAY P., ALYANAKIAN M.A., ROUDIÈRE L., THERBY A., CHAIX M.L., DUPONT B., POL S., VIARD J.P.**

Prevalence of mixed cryoglobulins in relation to CD4 cell count among patients coinfecting with HIV and hepatitis C virus.

*Clin. Infect. Dis.*, 40 (2), 306-308, 2005

(Services cités : Hépatologie Adulte, Infectiologie, U580)

**AARON L., LEBRAY P., ALYANAKIAN M.A., ROUDIÈRE L., THERBY A., CHAIX M.L., DUPONT B., POL S., VIARD J.P.**

Reply to Perrella et al.

*Clin. Infect. Dis.*, 40 (11), 1708-1709, 2005

(Services cités : Hépatologie Adulte, Infectiologie, Laboratoire d'Immunologie)

**BRIAT A., DULIOUST E., GALIMAND J., FONTAINE H., CHAIX M.L., LETUR-KONIRSCH H., POL S., JOUANNET P., ROUZIOUX C., LERUEZ-VILLE M.**

Hepatitis C virus in the semen of men coinfecting with HIV-1: prevalence and origin.

*AIDS*, 19 (16), 1827-1835, 2005

(Services cités : CECOS, Laboratoire de Microbiologie, Hépatologie Adulte)

**OBJECTIVE::** To compare the prevalence of hepatitis C (HCV) RNA in semen from men infected with HCV and those coinfecting with HIV-1/HCV and to study the origin of HCV shed in semen. **DESIGN::** Two prospective studies (HC EP09 and BINECO) included 120 HCV-positive men, 82 coinfecting with HIV-1; all had positive HCV RNA detection in blood. **METHODS::** Paired blood and semen samples were collected for HCV RNA detection and quantification in seminal plasma and in blood serum; repeated semen samples were obtained for 45 men. HCV RNA was sought in spermatozoa and non-sperm cells. Phylogenetic analysis of the HVR-1 region of HCV compared the quasispecies in blood serum and seminal plasma of two men. **RESULTS::** HCV RNA was more frequently found in the semen of men coinfecting with HIV-1 (37.8%) than in those with only HCV infection (18.4%) ( $P = 0.033$ ). HCV RNA detection in semen was intermittent and was positive in at least one semen sample of 42.8% of HIV-1/HCV-coinfecting men who provided repeated samples. Men with HCV-positive semen had significantly higher HCV load in blood than men with HCV-negative semen ( $P = 0.038$ ). Phylogenetic comparison of HCV quasispecies in blood and in semen showed no evidence of HCV replication in genital leukocytes; however, a phenetic structure was observed between compartments ( $P < 0.001$ ). **CONCLUSIONS::** HCV particles in semen originate from passive passage from blood, with preferential transfer of some variants. Nearly half of HIV-1/HCV-coinfecting men may intermittently harbour HCV in their semen. Recommendations of protected sex for HIV-infected individuals should be reinforced.

**CACOUB P., SAADOUN D., BOURLIERE M., KHIRI H., MARTINEAU A., BENHAMOU Y., VARASTET M., POL S., THIBAUT V., ROTILY M., HALFON P.**

Hepatitis B virus genotypes and extrahepatic manifestations.

*J. Hepatol.*, 43 (5), 764-770, 2005

(Services cités : Hépatologie Adulte)

**BACKGROUND/AIMS:** This study aimed at correlating the presence of extrahepatic manifestations with hepatitis B virus (HBV) genotypes in patients with chronic HBV infection. **METHODS:** This was a national (France), multicenter, retrospective, cross-sectional study. HBV genotypes were determined in 190 patients HBsAg-positive for at least 6 months and documented before any treatment. **RESULTS:** Patients were aged 42 $\pm$ 15 years and mainly male (77%). Alcohol intake was high in 6% of them, ALT elevated in 73%; 27% were cirrhotic. All HBV genotypes were found, mainly A (24%), D (29%), C (11%), and E (10%). Thirty (16%) patients had clinical extrahepatic manifestations, mainly sensory-motor deficiency, sicca syndrome, myalgia, glomerulonephritis, and arthralgia-arthritis. Their presence was not related to any epidemiologic, viral (including genotypes) or hepatic factor, but to a higher platelet count ( $P=0.004$ ). Twenty-nine (15%) patients had biological extrahepatic manifestations, mainly anti-smooth muscle, antinuclear, and anti-nucleosome antibodies. Their presence was related only to anti-HBe antibodies positivity ( $P=0.007$ ) or elevated platelet count ( $P=0.003$ ). Carrying precore mutant HBV increased by 2.8 folds the risk to have at least one extrahepatic biological

manifestation. **CONCLUSIONS:** No relationships between HBV genotypes and the presence of extrahepatic manifestations were evidenced in patients with chronic HBV infection.

**CACOUB P., POL S.**

Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) coinfection: epidemiology, severity and recent therapeutic strategies.

*Rev. Méd. Interne*, 26 (4), 267-270, 2005

(Services cités : Hépatologie Adulte)

**DHARANCY S., MALAPEL M., PERLEMUTER G., ROSKAMS T., CHENG Y., DUBUQUOY L., PODEVIN P., CONTI F., CANVA V., PHILIPPE D., GAMBIEZ L., MATHURIN P., PARIS J.C., SCHOONJANS K., CALMUS Y., POL S., AUWERX J., DESREUMAUX P.**

Impaired expression of the peroxisome proliferator-activated receptor alpha during hepatitis C virus infection.

*Gastroenterology*, 128 (2), 334-342, 2005

(Services cités : Hépatologie Adulte, U370)

**Background & Aims:** Liver inflammation, fibrosis, and dyslipidemia are common features in patients with chronic hepatitis C virus (HCV) infection. Because peroxisome proliferator-activated receptor alpha (PPARalpha) is highly expressed in the liver and is involved in the regulation of lipid metabolism and inflammation, we sought to determine whether HCV infection may locally impair PPARalpha expression and activity. **Methods:** PPARalpha expression was investigated in liver biopsy specimens of 86 untreated patients with HCV infection and controls, by using real-time polymerase chain reaction (PCR), Western blot analysis, and immunohistochemistry. PPARalpha activity was assessed by quantification of the key gene target carnitine palmitoyl acyl-CoA transferase 1 (CPT1A) messenger RNA (mRNA). The influence of HCV core protein on PPARalpha mRNA expression was analyzed in vitro by real-time PCR in HCV core-expressing HepG2 cells activated with the PPARalpha ligand fenofibric acid. **Results:** Hepatic concentrations of PPARalpha and CPT1A expressed by hepatocytes were impaired profoundly in the livers of untreated patients with HCV infection compared with controls. A mean decrease of 85% in PPARalpha mRNA expression paralleled with a lack of CPT1A mRNA induction also were observed in HCV core-expressing HepG2 cells compared with controls. **Conclusions:** HCV infection is related to altered expression and function of the anti-inflammatory nuclear receptor PPARalpha. These results identify hepatic PPARalpha as one mechanism underlying the pathogenesis of HCV infection, and as a new therapeutic target in traditional treatment of HCV-induced liver injury.

**FARTOUX L., POL S., SERFATY L.**

L'irréversibilité de la cirrhose : "un dogme bousculé".

*Rev. Prat.*, 55 (14), 1549-1551, 2005

(Services cités : Hépatologie Adulte)

**FONTAINE H., VALLET-PICHARD A., CHAIX M.L., CURRIE G., SERPAGGI J., VERKARRE V., VARAUT A., MORALES E., NALPAS B., BROSGART C., POL S.**

Efficacy and safety of adefovir dipivoxil in kidney recipients, hemodialysis patients, and patients with renal insufficiency.

*Transplantation*, 80 (8), 1086-1092, 2005

(Services cités : Anatomo-Pathologie, Hépatologie Adulte, Laboratoire de Microbiologie)

**BACKGROUND.:** This study analyzes the biochemical, serological, and virological efficacy and the safety of adefovir dipivoxil in patients with renal disturbances. **METHODS.:** Twelve patients with lamivudine-resistant hepatitis B virus (HBV) chronic infection were treated for a median time of 15 (3-19) months. The daily dosage was 10 mg initially and then adjusted according to renal function. **RESULTS.:** Median (range) ALT values remained stable: 55 (13-117) and 37 (17-266) UI/L. After the 12th month, the median decline in serum HBV DNA was from 8.76 (6.3-9.7) to 2.97 (1.15-5.65) log<sub>10</sub> Eq/ml (median decline of -5.5 log<sub>10</sub>). No virologic breakthrough was observed. One of the six HBeAg-positive patients lost HBe Ag but without HBe seroconversion; none had HBs Ag loss. There were no significant clinical and biochemical adverse effects. In the 11 nonhemodialysed patients, the creatinine clearance significantly improved from 70 (30-100) to 88 (38-125) ml/mn (P=0.01) and the mean serum creatinine levels increased only slightly from 114 (91-839) to 130 (81-561) μmol/ml (NS). Serum phosphorus remained stable. The urinary level of protein decreased from 0.16 (0.08-8.63) to 0.12 (0.01-0.74) g/day (NS). **CONCLUSIONS.:** Adefovir dipivoxil is safe for the treatment of chronic hepatitis B in patients with varying degrees of renal dysfunction and lamivudine-resistant HBV and results in biochemical and virological efficacy similar to that reported in the general population.

**FONTAINE H., VALLET-PICHARD A., POL S.**

Histopathological efficacy of ribavirin monotherapy in hepatitis C virus positive renal transplant patients.

*Transplantation*, 79 (12), 1771, 2005

(Services cités : Hépatologie Adulte)

**LEBRAY P., NALPAS B., VALLET-PICHARD A., BROISSAND C., SOBESKY R., SERPAGGI J., FONTAINE H., POL S.**

The impact of haematopoietic growth factors on the management and efficacy of antiviral treatment in patients with hepatitis C virus.

*Antivir. Ther.*, 10 (6), 769-776, 2005

(Services cités : Hépatologie Adulte)

**AIM:** To evaluate the benefits of haematopoietic growth factors (HGFs) during the treatment of chronic hepatitis C virus (HCV) infection with severe haematotoxicity. **METHODS:** This was a 1-year retrospective study of HCV-positive patients receiving pegylated interferon and ribavirin. Patients received different HGFs, depending on certain criteria: they received erythropoietin (EPO) when their haemoglobin (Hb) levels were less than 10 g/dl and granulocyte colony-stimulating factor (G-CSF) when their neutrophil count was less than 750 cells/mm<sup>3</sup>.

Haematological data, adherence and virological response were analysed and compared according to HGF use. **RESULTS:** In total, 132 patients were studied and 31 (23.5%) required HGF. Under multivariate analysis, baseline Hb levels of less than 13g/dl or a drop in Hb levels of over 2% per week predicted severe anaemia, and a baseline neutrophil count under 2900/mm<sup>3</sup> predicted severe neutropaenia. HGF administration restored Hb values and the neutrophil count to above 10 g/dl and 1500 cells/mm<sup>3</sup>, respectively, in all 31 patients. Adherence to antiviral treatment was achieved in 25% of patients versus 58% of controls without severe haematotoxicity. The primary and sustained virological response did not differ statistically between HGF support and the control group (61% versus 57% and 32% versus 39%, respectively). **CONCLUSION:** HGF administration counteracts the severe haematological adverse effects which occur during antiviral therapy and maintains the rate of sustained response.

**LINO M., BINAUT R., NOEL L.H., PATEY N., RUSTIN P., DANIEL L., SERPAGGI J., VARAUT A., VANHILLE P., KNEBELMANN B., GRUNFELD J.P., FAKHOURI F.**

Tubulointerstitial nephritis and fanconi syndrome in primary biliary cirrhosis.

*Amer. J. Kidney Dis.*, 46 (3), e41-e46, 2005

(Services cités : Hépatologie Adulte, Néphrologie Adulte)

Primary biliary cirrhosis is a chronic cholestatic liver disease of unknown cause that predominantly affects middle-aged women. Distal tubular acidosis is the main renal complication of primary biliary cirrhosis. Tubulointerstitial nephritis and Fanconi syndrome have been reported more rarely. We report on 2 patients with primary biliary cirrhosis who presented with tubulointerstitial nephritis and Fanconi syndrome and review similar cases published previously. Serum from 1 patient exerted an inhibitory effect on pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase, 2 mitochondrial enzymes that are the main targets of antimitochondrial antibodies in primary biliary cirrhosis. Antimitochondrial antibodies may have a role in the genesis of tubulointerstitial nephritis and Fanconi syndrome, 2 typical renal features of mitochondrial cytopathies. Tubulointerstitial nephritis and Fanconi syndrome have to be added to the spectrum of renal diseases associated with primary biliary cirrhosis.

**PAYAN C., ROUDOT-THORAVAL F., MARCELLIN P., BLED N., DUVERLIE G., FOUCHARD-HUBERT I., TRIMOULET P., COUZIGOU P., COINTE D., CHAPUT C., HENQUELL C., ABERGEL A., PAWLOTSKY J.M., HEZODE C., COUDE M., BLANCHI A., ALAIN S., LOUSTAUD-RATTI V., CHEVALLIER P., TREPO C., GEROLAMI V., PORTAL I., HALFON P., BOURLIERE M., BOGARD M., PLOUVIER E., LAFFONT C., AGIUS G., SILVAIN C., BRODARD V., THIEFIN G., BUFFET-JANVRESSE C., RIACHI G., GRATARD F., BOURLET T., STOLL-KELLER F., DOFFOEL M., IZOPET J., BARANGE K., MARTINOT-PEIGNOUX M., BRANGER M., ROSENBERG A., SOGNI P., CHAIX M.L., POL S.**

Changing of hepatitis C virus genotype patterns in France at the beginning of the third millenium: The GEMHEP GenoCII Study.

*J. Viral Hepat.*, 12 (4), 405-413, 2005

(Services cités : Hépatologie Adulte, Laboratoire de Microbiologie)

Summary. This cross-sectional study aimed to investigate, during a short period between 2000 and 2001, in a large population of patients with chronic hepatitis C, the epidemiological characteristics of hepatitis C virus (HCV) genotypes in France. Data from 26 referral centres, corresponding to 1769 patients with chronic hepatitis C were collected consecutively during a 6-month period. HCV genotyping in the 5'-non-coding region (NCR) was performed in each center using the line probe assay (LiPA, in 63% of cases), sequencing (25%) or primer-specific polymerase chain reaction (PCR) (12%). HCV genotypes 1a, 1b, 2, 3, 4, 5, non-subtyped 1 and mixed infection were found in 18, 27, 9, 21, 9, 3, 11 and 1% of our population, respectively. HCV genotype distribution was associated with gender, age, source and duration of infection, alanine aminotransferase (ALT) levels, cirrhosis, alcohol consumption, hepatitis B virus (HBV) and human immunodeficiency virus (HIV) coinfection. In multivariate analysis, only the source of infection was the independent factor significantly associated with genotype ( $P = 0.0001$ ). In conclusion, this study shows a changing pattern of HCV genotypes in France, with i.v. drug abuse as the major risk factor, an increase of genotype 4, and to a lesser extent 1a and 5, and a decrease of genotypes 1b and 2. The modification of the HCV genotype pattern in France in the next 10 years may require new therapeutic strategies, and further survey studies.

**POL S.**

Treatment of delta (type D) hepatitis 384.

*Gastroentérol. Clin. Biol.*, 29 (4), 384-387, 2005

(Services cités : Hépatologie Adulte, U370)

**POL S.**

Epidemiology and natural history of hepatitis B infection.

*Rev. Prat.*, 55 (6), 599-606, 2005

(Services cités : Hépatologie Adulte)

The transmission of the hepatitis B virus (HBV) is parenteral, sexual and perinatal. If a fulminant hepatitis may occur in 1% of cases of symptomatic acute hepatitis, the main problem of HBV infection is its chronicity, as defined by HBs antigen carriage for more than 6 months. It occurs in only 0.5 to 3% of immunocompetent adults but more frequently in children (up to 90%) or in immunocompromised patients (30 to 100%). Evolution of HBV chronic infection is characterized by variations of viral replication with spontaneous reactivations or discontinuations with potential clinical and biochemical exacerbations. Pathogeny of HBV infection is mainly immune-mediated, resulting from the host-virus interactions but also from the complexity of HBV (integration, mutation, occult replication), explaining the polymorphism of chronic HBV infection; it includes immune tolerance, inactive carriage of HBs antigen but also immune elimination with chronic active hepatitis which may lead to cirrhosis (yearly incidence of 1.3 to 5.9%). Cirrhosis may result in complications of portal hypertension and liver failure or hepatocellular carcinoma which explain 80% of morbidity and mortality of HBV: the 5-year survival of HBV-related cirrhosis ranges from 52 to 82%. Immunosuppression, delta virus superinfection or chronic alcohol consumption are the main factors which modify the natural history of HBV infection. HBV chronic infection is a problem of public health, particularly in developing countries, evidencing the need for universal HBV vaccination.

**VARAUT A., FONTAINE H., SERPAGGI J., VERKARRE V., VALLET-PICHARD A., NALPAS B., IMBERTBISMUTH F., LEBRAY P., POL S.**

Diagnostic accuracy of the fibrotest in hemodialysis and renal transplant patients with chronic hepatitis C virus.

*Transplantation*, 80 (11), 1550-1555, 2005

(Services cités : Hépatologie Adulte, U370)

**BACKGROUND.:** An accurate diagnosis of hepatitis C virus (HCV)-related liver lesions is mandatory in dialysis patients and kidney recipients to better define the treatment of and contraindications to kidney transplantation. The aim of this study was to assess the diagnostic accuracy of the fibrotest (a noninvasive method to assess liver fibrosis in HCV on a scale from 0 to 1) in hemodialysis and renal transplant patients infected by chronic HCV. **METHODS.:** In all, 110 patients with biopsy-proven HCV (60 renal transplant recipients and 50 hemodialysis patients), determined using the METAVIR scoring system, were studied. **RESULTS.:** Forty-six percent of patients had fibrosis  $\geq$ F2. A positive predictive value of a score  $>0.6$  for the presence of significant fibrosis by comparison with liver biopsy was 71%, and a negative predictive value of  $<0.2$  for excluding significant fibrosis was 77%, respectively. The areas under the ROC curves for the diagnosis of significant fibrosis were 0.66, 0.47, and 0.71 in the global population, hemodialysis patients, and renal transplant patients, respectively. In all, 75% of patients were correctly classified using the fibrotest. If biopsy was restricted to scores in the intermediate range

(<0.6 and >0.2), the index could reduce the indication for biopsy by 47%. The results did not differ significantly in hemodialysis and renal transplant patients. CONCLUSION.: The fibrotest has a diagnostic value in hemodialysis and renal transplant patients which is similar to that reported in the general population (75%) and its use could avoid 32% of liver biopsies if it were interpreted in detail in nephrology patients.

**YAZDANPANA H Y., de CARLI G., MIGUERES B., LOT F., CAMPINS M., COLOMBO C., THOMAS T., DEUFFIC-BURBAN S., PREVOT M.H., DOMART M., TARANTOLA A., ABITEBOUL D., DENY P., POL S., DESENCLOS J.C., PURO V., BOUVET E.**

Risk factors for hepatitis C virus transmission to health care workers after occupational exposure: a European case-control study.

*Clin. Infect. Dis.*, 41 (10), 1423-1430, 2005

(Services cités : Hépatologie Adulte, U370)

BACKGROUND: Additional studies are required to identify risk factors for hepatitis C virus (HCV) transmission to health care workers after occupational exposure to HCV. METHODS: We conducted a matched case-control study in 5 European countries from 1 January 1991 through 31 December 2002. Case patients were health care workers who experienced seroconversion after percutaneous or mucocutaneous exposure to HCV. Control subjects were HCV-exposed health care workers who did not experience seroconversion and were matched with case patients for center and period of exposure. RESULTS: Sixty case patients and 204 control subjects were included in the study. All case patients were exposed to HCV-infected fluids through percutaneous injuries. The 37 case patients for whom information was available were exposed to viremic source patients. As risk factors for HCV infection, multivariate analysis identified needle placement in a source patient's vein or artery (odds ratio [OR], 100.1; 95% confidence interval [CI], 7.3-1365.7), deep injury (OR, 155.2; 95% CI, 7.1-3417.2), and sex of the health care worker (OR for male vs. female, 3.1; 95% CI, 1.0-10.0). Source patient HCV load was not introduced in the multivariate model. In unmatched univariate analysis, the risk of HCV transmission increased 11-fold for health care workers exposed to source patients with a viral load >6 log(10) copies/mL (95% CI, 1.1-114.1), compared with exposures to source patients with a viral load < or =4 log10 copies/mL. CONCLUSION: In this study, HCV occupational transmission was found to occur after percutaneous exposures. The risk of HCV transmission after percutaneous exposure increased with deep injuries and procedures involving hollow-bore needle placement in the source patient's vein or artery. These results highlight the need for widespread adoption of needlestick-prevention devices in health care settings, together with other preventive measures.

**2004**

**ABERGEL A., DARCHA C., CHEVALLIER M., UGHETTO S., HENQUELL C., POL S., de LEDINGHEN V., CANVA V., BRONOWICKI J.P., TRAN A., MARTINEAU N., LAFEUILLE H., DECHELOTTE P., BOMMELAER G., BONNY C.**

Histological response in patients treated by interferon plus ribavirin for hepatitis C virus-related severe fibrosis.

*Eur. J. Gastroenterol. Hepatol.*, 16 (11), 1219-1227, 2004

(Services cités : Hépatologie Adulte)

BACKGROUND: Studies of viral hepatitis C have suggested that fibrosis can regress, at least in patients with sustained virological response. A recent study suggested that cirrhosis was reversible in sustained and non-virological responders. AIM: To study fibrosis progression rate and cirrhosis reversion in patients treated for severe fibrosis with interferon or interferon +

ribavirin. PATIENTS AND METHODS: Ninety-nine patients were treated with interferon + ribavirin and 64 with interferon. The Metavir fibrosis score and the semiquantitative fibrosis score (SFS) were used to assess fibrosis. RESULTS: In sustained responders, fibrosis progression rate decreased from 0.26 Metavir unit (interquartile range: 0.19-0.34) to -0.67 (-0.67 to 0) ( $P < 0.0001$ ) and from 0.81 SFS unit (0.48-1.13) to -1.33 (-3.67 to 0) ( $P < 0.0001$ ). In non-responders, fibrosis progression rate decreased from 0.25 Metavir unit (0.17-0.33) before treatment to 0 (0-0) during treatment ( $P = 0.002$ ) and from 0.63 SFS unit (0.49-1.12) to 0 (-2.67-1.33) ( $P = 0.18$ ). Six out of 18 (33%) sustained virological responders and four of 43 (9%) non-responders regressed from cirrhosis (F4) to severe fibrosis (F3) ( $P = 0.058$ ). No patient with cirrhosis had a decrease of Metavir fibrosis score of 2 points. CONCLUSION: Interferon can slow fibrosis progression in sustained virological responders with severe fibrosis. In patients with a non-virological response and treated for 12 months the fibrosis progression rate was nil, meaning that only fibrosis stabilization could be obtained in these patients. Then, longer treatment duration (3-4 years) could be evaluated in non-virological responders.

### **BRECHOT C.**

Pathogenesis of hepatitis B virus-related hepatocellular carcinoma: old and new paradigms.

*Gastroenterology*, 127 (5 Suppl 1), S56-S61, 2004

(Services cités : Hépatologie Adulte, U370)

Chronic infection with the hepatitis B virus (HBV) is a major risk factor for development of hepatocellular carcinoma (HCC). The pathogenesis of cancer in HBV infection has been extensively analyzed, and multiple factors appear to play a role. A major factor is chronic inflammation and the effects of cytokines in the development of fibrosis and liver cell proliferation. Also important is the role of integration of HBV DNA into host cellular DNA, which, in some situations, acts to disrupt or promote expression of cellular genes that are important in cell growth and differentiation. In addition, expression of HBV proteins may have a direct effect on cellular functions, and some of these gene products can favor malignant transformation. Several HBV genes have been found in infected tissues more frequently than others, including truncated pre-S2/S, hepatitis B X gene, and a novel spliced transcript of HBV, referred to as the hepatitis B spliced protein. The proteins expressed from these integrated genes have been shown to have intracellular activities that may account for their association with HCC, including effects on cellular growth and apoptosis. Finally, some patients with HCC have no detectable hepatitis B surface antigen in serum but do have low levels of HBV DNA in serum and integrated molecules of HBV DNA in tissue. Occult HBV infection may account for a proportion of cases of HCC that occur in patients without serologic markers for hepatitis B and C and may be a cofactor in HCC in patients with chronic hepatitis C who have coexistent occult HBV infection.

### **CORREAS J.M., VALLET-PICHARD A., POL S., HELENON O.**

The role of contrast-enhanced ultrasonography for the detection of hepatocellular carcinoma.

*J. Radiol.*, 85 (5 Pt 2), 690-703, 2004

(Services cités : Hépatologie Adulte, Radiologie Adulte)

The incidence of the hepatocellular carcinoma (HCC) is increasing in Occident, as well as in France. Primary prevention is the only solution for early detection. The combination of ultrasound (US) and alphaFP each 4 to 6 Months dosage has many limitations. The sensitivity of US examination is rather poor (less than 70% for lesions below 2 cm in diameter) and serum alphaFP values remain normal in almost 50% of HCC. US contrast agents (USCAs) with

perfluorocarbon gases increase the backscattered signals during all phases of the liver transit, including arterial, portal and delayed phases. Hepatocellular lesions exhibit a specific kinetics with strong enhancement during arterial phase, and rapid wash-out during portal and delayed phases. USCAs increase the detection of HCCs and allow characterization of additional focal lesions found in cirrhotic livers (regenerative and dysplastic nodules, haemangiomas.). Indeed, regenerative nodules contrast uptake is synchronous to the surrounding parenchyma, and usually disappear during portal and delayed phases. However, US in cirrhosis remains a difficult examination, with limitations due to limited access to sub-diaphragmatic localization, attenuation of the ultrasound beam and shortness of the arterial phase.

**FONTAINE H., VALLET-PICHARD A., EQUI-ANDRADE C., NALPAS B., VERKARRE V., CHAIX M.L., LEBRAY P., SOBESKY R., SERPAGGI J., KREIS H., POL S.**

Histopathologic Efficacy of Ribavirin Monotherapy in Kidney Allograft Recipients with Chronic Hepatitis C.

*Transplantation*, 78 (6), 853-857, 2004

(Services cités : Anatomo-Pathologie, Hépatologie Adulte, Laboratoire de Microbiologie, Transplantation & Réanimation Adulte, U370)

**BACKGROUND.:** The deterioration of chronic hepatitis C is frequent in kidney recipients and results in a decrease in survival of patients and allografts. Interferon is contraindicated because of the risk of rejection and its low efficacy. The aim of this study was to analyze the biologic, virologic, and histopathologic efficacy of ribavirin alone in kidney allograft recipients with hepatitis C. **METHODS.:** Thirteen kidney recipients (eight men and five women, 46+/-11 years of age) with severe Metavir score of fibrosis (eight F3 and five F4) were treated with ribavirin alone during 22.4+/-13.9 months. Liver biopsy was performed before and during therapy, with a mean interval time of 5.7+/-9.3 years. **RESULTS.:** The transaminase level decreased significantly (128+/-77 vs. 53+/-28, P=0.001) without significant change of serum quantitative hepatitis C virus load. The comparison of pretreatment and on-treatment biopsy specimens showed a significant decrease in the activity Metavir score (1.23+/-1.01 vs. 2.46+/-0.78, P=0.05) and a nonsignificant trend for a decrease in the fibrosis score. Ribavirin tolerance was fair, and only one patient required erythropoietin therapy. **CONCLUSIONS.:** Ribavirin alone in kidney allograft recipients results in biologic and histologic improvement without a virologic response and is reasonably well tolerated.

**GEROLAMI R., UCH R., FAIVRE J., GARCIA S., HARDWIGSEN J., CARDOSO J., MATHIEU S., BAGNIS C., BRECHOT C., MANNONI P.**

Herpes simplex virus thymidine kinase-mediated suicide gene therapy for hepatocellular carcinoma using HIV-1-derived lentiviral vectors.

*J. Hepatol.*, 40 (2), 291-297, 2004

(Services cités : Hépatologie Adulte)

**BACKGROUND/AIMS:** Gene therapy is a promising approach for treatment of hepatocellular carcinoma (HCC). However, transduction of non-tumoral hepatocytes may lead to severe hepatitis when using suicide gene therapy approaches. The aim of our study was to evaluate the gene transfer efficiency into HCC cells and normal hepatocytes using human immunodeficiency virus (HIV)-derived lentiviral vectors in vitro and in vivo. **METHODS:** Lentiviral vectors encoding for the LacZ gene or the fusion gene HSV-Tk/GFP were tested in vitro in human HCC cells and human hepatocytes in primary culture and in vivo in a chemically induced rat model of HCC. **RESULTS:** We show that HIV-1-derived lentiviral vectors are efficient in transducing

HCC cells in vitro and in vivo. No significant transduction of non-tumorous hepatocytes was observed in vivo whatever the route of administration used. Measurement of tumor growth following direct intratumoral injection of a lentiviral vector containing the HSV-Tk gene and GCV treatment showed a strong antitumoral efficacy in the absence of normal liver toxicity. CONCLUSIONS: These observations suggest that lentiviral vectors allow an antitumoral effect with low liver toxicity when using suicide gene therapy approach and could be efficient tools for HCC gene therapy.

**KOMURIAN-PRADEL F., RAJOHARISON A., BERLAND J.L., KHOURI V., PERRET M., VAN ROOSMALEN M., POL S., NEGRO F., PARANHOS-BACCALA G.**

Antigenic relevance of F protein in chronic hepatitis C virus infection.

*Hepatology*, 40 (4), 900-999, 2004

(Services cités : Hépatologie Adulte)

The hepatitis C virus (HCV) F protein is a recently described, frameshift product of HCV core encoding sequence of genotype 1a. Its function and antigenic properties are unknown. Using enzyme-linked immunosorbent assay, we assessed the prevalence of anti-F antibodies in 154 patients chronically infected with HCV, 65 patients with other liver diseases, and 121 healthy controls. For this purpose, we expressed a highly purified HCV F recombinant protein from HCV genotype 1a in *Escherichia coli*. Because the F protein shares the 10 first amino acids with the core protein, the anti-HCV F response was also assessed by a F recombinant protein deleted of its 10 first amino acids [Delta(1-10)-F]. Ninety-six (62%) of the 154 HCV serum samples reacted with the complete F recombinant protein, whereas 39 (25%) showed a weaker anti-Delta(1-10)F reactivity and 150 (97%) had anti-core antibodies. No reactivity against F, Delta(1-10)F, or core was detected in any of the controls. To exclude a potential cross-reaction of anti-F antibodies with anti-core antibodies, a specific enzyme-linked immunosorbent assay was performed for anti-core antibodies. The specificity of anti-F antibodies was confirmed using an F synthetic peptide. The prevalence of anti-F antibodies did not correlate with HCV RNA serum level, genotype, or stage of liver disease. Sequence analysis from 8 anti-F-positive and 5 anti-F-negative serum samples did not reveal any particular difference potentially accounting for their respective anti-F responses. In conclusion, the F protein elicits specific antibodies in 62% of individuals chronically infected with HCV; such anti-F response does not seem to be affected by the F sequence heterogeneity.

**LEBRAY P., ZYLBERBERG H., HUE S., POULET B., CARNOT F., MARTIN S., CHRETIEN Y., POL S., CAILLAT-ZUCKMAN S., BRECHOT C., NALPAS B.**

Influence of HFE gene polymorphism on the progression and treatment of chronic hepatitis C.

*J. Viral Hepat.*, 11 (2), 175-182, 2004

(Services cités : U370, U580, Hépatologie Adulte, Anatomopathologie, Laboratoire d'Immunologie)

We analysed liver histology findings in a large cohort of patients with chronic hepatitis C and in roughly half of them their response to interferon-alpha-based on iron parameters and HFE status. Histological activity and virological response to antiviral therapy (n = 146) were analysed in 273 immunocompetent and nonalcoholic patients with chronic hepatitis C, in terms of serum iron load, intrahepatic iron load (n = 110) and HFE mutations. Patients who were heterozygous for the C282Y and H63D mutations exhibited higher iron serum parameters than subjects without these mutations. The intrahepatic iron load was higher in H63D patients only. No association was observed between HFE mutations and histological activity. Increased iron parameters were

associated with liver disease severity by univariate analysis only. Genotype 1 and ferritinaemia were associated with a poor response to antiviral therapy, whereas the H63D mutation emerged as a positive predictive factor for end of treatment and sustained antiviral response. Therefore, in chronic hepatitis C patients serum and intrahepatic iron levels were weakly correlated with histological activity, while HFE mutations were not. As for the response to interferon-alpha, elevated ferritinaemia constituted a negative predictive factor whereas the H63D mutation was a positive one. The H63D mutation might form part of an immunogenetic profile influencing the response to interferon therapy.

**MANCINI-BOURGINE M., FONTAINE H., SCOTT-ALGARA D., POL S., BRECHOT C., MICHEL M.L.**

Induction or expansion of T-cell responses by a hepatitis B DNA vaccine administered to chronic HBV carriers.

*Hepatology*, 40 (4), 874-882, 2004

(Services cités : Hépatologie Adulte)

Despite the availability of effective hepatitis B vaccines for many years, over 370 million people remain persistently infected with hepatitis B virus (HBV). Viral persistence is thought to be related to poor HBV-specific T-cell responses. A phase I clinical trial was performed in chronic HBV carriers to investigate whether HBV DNA vaccination could restore T-cell responsiveness. Ten patients with chronic active hepatitis B nonresponder to approved treatments for HBV infection were given 4 intramuscular injections of 1 mg of a DNA vaccine encoding HBV envelope proteins. HBV-specific T-cell responses were assessed by proliferation, ELISpot assays, and tetramer staining. Secondary end points included safety and the monitoring of HBV viraemia and serological markers. Proliferative responses to hepatitis B surface antigen were detected in two patients after DNA injections. Few HBV-specific interferon gamma-secreting T cells were detectable before immunization, but the frequency of such responses was significantly increased by 3 DNA injections. Immunization was well tolerated. Serum HBV DNA levels decreased in 5 patients after 3 vaccine injections, and complete clearance was observed in 1 patient. In conclusion, this study provides evidence that HBV DNA vaccination is safe and immunologically effective. We demonstrate that DNA vaccination can specifically but transiently activate T-cell responses in some chronic HBV carriers who do not respond to current antiviral therapies.

**POL S., LEBRAY P., VALLET-PICHARD A.**

HIV infection and hepatic enzyme abnormalities: intricacies of the pathogenic mechanisms.

*Clin. Infect. Dis.*, 38 Suppl 2 S65-S72, 2004

(Services cités : Hépatologie Adulte, U370)

Liver enzyme elevations are common in human immunodeficiency virus (HIV)-infected patients, and their diagnosis or management may be difficult because of the intricacies of the pathogenic mechanisms involved. These include hepatotoxicity related to the highly active antiretroviral therapy (HAART) regimen, idiosyncratic or immunoallergic mechanisms, and direct cytotoxicity enhanced by an underlying liver disease. Liver enzyme abnormalities may also reflect hepatitis B (HBV) or hepatitis C (HCV) infection, which each have their own risks for chronic immune-mediated liver disease (including hepatitis flare after immune reconstitution) and of direct cytotoxicity. Finally, other factors may affect liver deterioration, including alcohol-related liver disease, nonalcoholic steatohepatitis associated with metabolic syndromes (e.g., hyperlipidemia, diabetes, or being overweight) that are potentially HAART related, and use of medication or illicit drugs (e.g., methamphetamine). A better understanding of these complex interactions,

including adjustments of dosages of antiretroviral drugs, will probably help in the management of HIV-infected patients with liver enzyme abnormalities.

**POL S., CARNOT F., NALPAS B., LAGNEAU J.L., FONTAINE H., SERPAGGI J., SERFATY L., BEDOSSA P., BRECHOT C.**

Reversibility of hepatitis C virus-related cirrhosis.

*Hum. Pathol.*, 35 (1), 107-112, 2004

(Services cités : Hépatologie Adulte)

The aim of this retrospective study was to determine the potential reversibility of hepatitis C virus (HCV) cirrhosis with the combined antifibrotic effects of interferon-alpha and the increasing frequency of sustained virologic response. Sixty-four HCV-cirrhotic immunocompetent patients who underwent antiviral therapies (interferon-alpha with or without ribavirin) and pretreatment and posttreatment liver biopsies were included (group 1). Resolution of cirrhosis was defined as a decrease in the fibrosis score from 4 to 2 or less by the Metavir score after blinded analysis by 2 independent pathologists. An additional group of 4 HCV-infected dialysis patients (group 2) who had received antiviral treatment, among whom 3 underwent a combined renal and liver transplantation allowing the analysis of the whole liver, was also studied. In 5 (all stage Child A) of the 64 cirrhotic patients (7.8%), the final biopsy showed only F2 to portal and periportal fibrosis with rare fibrous septa without nodule formation. Four of these 5 were complete sustained responders (negative PCR and normal ALT), and 1 was a relapser. In group 2, reversibility of cirrhosis was observed in 3 of the 4 patients and was clearly shown in 2 patients by the analysis of the whole-liver examination at the time of the hepatectomy preceding the transplantation. In conclusion, long-lasting suppression of the necroinflammatory activity of liver disease and/or antifibro-genetic effects of interferon-alpha may allow regression of cirrhosis.

**POL S.**

HCV treatments for HIV patients be treated? When and how ?

*Méd. Mal. Infec.*, 34 (Sup.2), 22-24, 2004

(Services cités : Hépatologie Adulte, U370)

**ROSMORDUC O., HERMELIN B., BOELLE P.Y., POUPON R.E., POUPON R., CHAZOILLERES O.**

ABCB4 gene mutations and primary sclerosing cholangitis.

*Gastroenterology*, 126 (4), 1220-1222, 2004

(Services cités : Hépatologie Adulte)

**VALLET-PICHARD A., POL S.**

Hepatitis viruses and human immunodeficiency virus co-infection: pathogenesis and treatment.

*J. Hepatol.*, 41 (1), 156-166, 2004

(Services cités : Hépatologie Adulte, U370)

**VONA G., ESTEPA L., BEROU D., DAMOTTE D., CAPRON F., NALPAS B., MINEUR A., FRANCO D., LACOUR B., POL S., BRECHOT C., PATERLINI-BRECHOT P.**

Impact of cytomorphological detection of circulating tumor cells in patients with liver cancer.

*Hepatology*, 39 (3), 792-797, 2004

(Services cités : U370, Hépatologie Adulte)

The clinical impact of circulating tumor cell (CTC) detection is controversial, mainly due to

drawbacks of molecular approaches applied to this field. We sought to determine if the specific identification and counting of circulating tumor cells by cytomorphologic analysis has clinical usefulness. Peripheral blood (6 mL), treated using isolation by size of epithelial tumor cells, was obtained from 44 patients with primary liver cancer (PLC) and without metastases, 30 patients with chronic active hepatitis, 39 with liver cirrhosis, and 38 healthy individuals, and followed up for a mean period of 1 year. We searched for beta-catenin mutations in 60 single microdissected CTCs. One patient with liver cancer developed extrahepatic metastases during follow-up. CTCs and microemboli were found in 23 of the 44 patients with liver cancer and in none of the patients with chronic active hepatitis, patients with cirrhosis, or healthy subjects. Their presence was significantly associated with tumor diffusion ( $P = .0001$ ) and portal tumor thrombosis ( $P = .006$ ). Both the presence ( $P = .01$ ) and number ( $P = .02$ ) of CTCs and microemboli were significantly associated with a shorter survival. beta-Catenin mutations were found in 3 of 60 CTCs, arguing against their impact on the initial step of tumor cell invasion. In conclusion, the highly sensitive and specific detection of CTCs and microemboli may have clinical implications for cancer staging and outcome prediction. We also show the feasibility of molecular studies of individual circulating tumor cells, aimed at identifying gene mutations involved in tumor invasion. (HEPATOLOGY 2004;39:792-797.)

**WERLE B., CINQUIN K., MARCELLIN P., POL S., MAYNARD M., TREPO C., ZOULIM F.**

Evolution of hepatitis B viral load and viral genome sequence during adefovir dipivoxil therapy. *J. Viral Hepat.*, 11 (1), 74-83, 2004

(Services cités : Hépatologie Adulte)

Phase II and III clinical trials of adefovir dipivoxil (ADV) for the treatment of chronic hepatitis B have shown that this hepadnavirus polymerase inhibitor is well tolerated and effectively suppresses hepatitis B virus (HBV) replication. We therefore analysed the evolution of viral load and the emergence of HBV polymerase mutants in a 22-patient subgroup from a phase III clinical trial of ADV for the treatment of HBeAg-positive chronic hepatitis B. HBV DNA serum titres were quantified using a real-time polymerase chain reaction (PCR) assay with molecular hybridization probes. Emergence of polymerase mutants was assessed by direct sequencing of the viral reverse transcriptase domain after PCR amplification of HBV DNA isolated from serum. Our results indicated that ADV therapy effectively suppressed HBV replication in these patients (median serum HBV decrease at week 48 of treatment = 4.3 log<sub>10</sub> copies/mL). The initial drop of HBV DNA titres in serum at week 12 of ADV therapy seemed to be predictive of subsequent HBe seroconversion ( $P = 0.059$ ). Neither viral breakthrough nor the selection of drug resistant mutants were observed during the study period. Our results showed that ADV administration for 48-72 weeks effectively suppresses HBV replication without the emergence of resistant viral mutants.

**2003**

**AGRET F., VALLET-PICHARD A., LANDAU A., CARNOT F., POL S.**

Late presentation of Wilson's disease as cirrhosis complicating hepatocellular carcinoma. *Gastroentérol. Clin. Biol.*, 27 (1), 130-131, 2003

(Services cités : Hépatologie Adulte)

**HALFON P., POL S., BOURLIERE M., COURCAMBECK J., CACOUB P.**

Nucleoside analogues resistance in the treatment of chronic hepatitis B virus infection.

*Rev. Méd. Interne*, 24 (12), 786-793, 2003

(Services cités : Hépatologie Adulte)

**SUBJECT:** Chronic hepatitis B virus (HBV) infection is usually treated by interferon alpha. However, a sustained response after stopping treatment is only obtained in 30% of patients.

**ACTUALITY:** New therapeutic nucleoside analogs have been developed, i.e. lamivudine, famciclovir, adefovir, entecavir, clevudine. However, as in HIV infection, clearance of the original hepatitis B virus with emergence of distinct resistant mutants have been observed during or after treatment with most nucleoside analogs. In this review, the underlying mechanisms of resistance and the characterisation of HBV mutants are described to optimize the best therapeutic regimen. **PERSPECTIVES:** Treatment of chronic HBV infection, as most of other chronic viral infection, should be based on combination therapy with a special search for the appearance of HBV mutant resistant.

**LEBRAY P., VALLET-RICHARD A., MICHEL M.L., FONTAINE H., SOBESKY R., BRECHOT C., POL S.**

Immunomodulatory drugs and therapeutic vaccine in chronic hepatitis B infection.

*J. Hepatol.*, 39 (Suppl.1), S151-S159, 2003

(Services cités : U370, Hépatologie Adulte)

**NALPAS B., COMBESURE C., PIERRE B., LEDENT T., GILLET C., PLAYOUST D., DANIEL T., BOZONNAT M.C., MARTIN S., BALMES J.L., DAURES J.P.**

Financial costs of alcoholism treatment programs : a longitudinal and comparative evaluation among four specialized centers.

*Alcohol. Clin. Exp. Res.*, 27 (1), 51-56, 2003

(Services cités : Hépatologie Adulte)

**BACKGROUND:** Alcoholism is a worldwide problem. Many strategies for alcohol detoxification and relapse prevention exist, but each alcohol treatment center has its own program. The objective of this study was to analyze and compare the financial cost and effectiveness of alcohol treatment programs from inpatient stay to follow-up 1 year later. This was a prospective, open, nonrandomized study of 4 specialized alcohol treatment centers and 267 patients admitted for alcohol detoxification. **METHODS:** We recorded all medical and nonmedical interventions related to the program during patient stay in the hospital and every 3 months after discharge for 1 year and recorded the occurrence of alcohol relapse. Financial evaluation was based on the prices of refund from the French national health insurance service. **RESULTS:** The mean cost of hospitalization ranged from 1326 euros to 1917 euros ( $p = 0.001$ ), a variation mainly due to the difference in the length of hospital stay but also to the cost of the inpatient program, routine medical checkups, and drugs administered. The mean cost of 1 year of follow-up per patient ranged from 419 euros to 1704 euros ( $p = 0.001$ ). The efficiency, corresponding to the money spent to prevent the relapse of one patient during 1 month, was approximately 500 euros/month in three centers and 658 euros in the fourth. However, for a similar efficiency, the effectiveness, assessed by the mean time without relapse, was significantly ( $p = 0.001$ ) different; center 1, which had the highest total cost, had an effectiveness 1.56 times higher than center 3, which had the lowest cost. **CONCLUSIONS:** This work emphasizes the heterogeneity of the costs and effectiveness of alcoholism treatment programs and suggests that research should be conducted to determine which program is the most rational, cost-efficient, and beneficial for patients and the public health office economy.

**NALPAS B., LEMAITRE R., DALBIES P.A., MONOD P., MARTIN S., BALMES J.L.**

Attitudes and opinions of private practitioners towards alcoholism. A survey in the Languedoc-Roussillon region.

*Presse Médicale*, 32 (9), 391-399, 2003

(Services cités : Hépatologie Adulte)

**OBJECTIVE:** Information on the position of private practitioners faced with the problem of alcoholism mainly concerns the role of the general practitioner in the follow-up of these patients and there is little information from private specialists, hence the need for new data **METHOD:** All the general practitioners and specialists in the Languedoc-Roussillon area were interviewed through a mailed questionnaire regarding their opinion on alcohol consumption and public health; their definition of the risks; moderate consumption and health; how they approached the question of drinking during consultations and their involvement in training and prevention. **RESULTS:** Six hundred sixty-five practitioners (12.4% of those interviewed) returned the questionnaire. The profile of those who replied was identical to that of the whole population surveyed. The medical corps is clearly aware of the need to fight against alcohol abuse, but this is associated with a relative ignorance of the basics of alcoholism, a non-systematic approach of the question of drinking during consultations, little involvement in its management, limited use of the specialised structures and limited training on the question. The specialists are less involved than the general practitioners, but appear more at ease when approaching the question of drinking with their patients and resort more frequently to specialised structures than the general practitioners. Continued medical training on alcoholism only concerned a minority of practitioners and its practical impact was low. **CONCLUSION:** With regard to alcoholism, the practitioners fulfill their role in providing medical care, within the limits of available therapeutic resources, but their role with regard to the reduction of the risks, i.e., primary or early prevention is more or less disregarded.

**PLAT A., YOUSSEF N., BROUSSE N., POL S.**

Liver and ageing: clinical characteristics.

*Gastroentérol. Clin. Biol.*, 27 (5), 540-547, 2003

(Services cités : Hépatologie Adulte, Anatomico-Pathologie)

**POL S.**

New recommendations for diagnosis and virological monitoring of viral hepatitis.

*Gastroentérol. Clin. Biol.*, 27 (1), 89, 2003

(Services cités : Hépatologie Adulte)

**POL S.**

Treatment of chronic hepatitis B today and tomorrow.

*Méd. Mal. Infec.*, 33 (Sup.A), 52-60, 2003

(Services cités : Hépatologie Adulte)

**PORTAL I., BOURLIERE M., HALFON P., de LEDINGHEN V., COUZIGOU P., BERNARD P.H., BLANC F., CAROLI-BOSC F., ARPURT J.P., VETTER D., MATHIEU-CHANDELIER C., CHAZOILLERES O., THIEFIN G., POL S., SOGNI P., ABERGEL A., BAILLY F., PICON M., DEBONNE J.M., ZAMORA C., ALLEMAN I., MOREAU X., DOLL F., EUGENE C., DUCLOUX S., LARREY D., OUZAN D., GRIMAUD J.C., GOUVERNET J., BOTTI G., GEROLAMI V., KHIRI H., GEROLAMI A., GAUTHIER**

**A.P., BOTTA-FRIDLUND D.**

Retreatment with interferon and ribavirin vs interferon alone according to viraemia in interferon responder-relapser hepatitis C patients: a prospective multicentre randomized controlled study.

*J. Viral Hepat.*, 10 (3), 215-223, 2003

(Services cités : Hépatologie Adulte)

Low pretreatment viral load has consistently been shown to be an independent predictor of sustained response (SR) in patients with chronic hepatitis C infection. We assessed the efficacy of interferon (IFN) plus ribavirin vs IFN alone in low viraemic patients (<2 millions copies/mL) who had relapsed to a previous course of IFN and the efficacy of 24 vs 48 week combination therapy in high viraemic patients. Two hundred and ninety-seven patients were randomly assigned to one of the four regimens after stratification on pretreatment viral load. All patients received IFN-a 2b (6 million units thrice weekly for 24 weeks and 3 million units thrice weekly for 24 weeks). Patients with low viraemia received either IFN-a 2b alone for 48 weeks (R1: 42 patients) or IFN-a 2b plus ribavirin (600 mg/day) for 24 weeks and IFN-a 2b alone for the next 24 weeks (R2: 48 patients). Patients with high viral load received either IFN-a 2b plus ribavirin for 24 weeks and then IFN-a 2b alone for the next 24 weeks (R3: 104 patients) or IFN-a 2b plus ribavirin for 48 weeks (R4: 103 patients). In low viraemic patients the rate of SR was 37.7% in group R1 and 59.6% in group R2 ( $P < 0.05$ ). In high viraemic patients, the rate of SR was 44.7% in group R3 and 51.4% in group R4 ( $P$ : NS). Thirty-one patients discontinued treatment (10.4%) without difference regarding treatment regimen. In the regimen using ribavirin we found no difference in terms of SR between patients receiving a dose of ribavirin below 10.6 mg/kg/day (55%) or over 10.6 mg/kg/day (58%). Histological improvement occurred in 70.2% of patients regardless of the regimen. Logistic regression showed that genotype 2 and 3, Knodell score <6 and alanine aminotransferase pretreatment level >3 x upper limit of normal were significantly and independently correlated with SR. In low viraemic patients who relapsed to a previous IFN treatment, combination therapy using high-dose IFN and low-dose ribavirin is better than high-dose IFN alone. In high viraemic patients there was no benefit in increasing the duration of combination therapy from 24 to 48 weeks. In this study, it was found that low dose of ribavirin can be used safely and there is no effect of ribavirin dose on SR.

**POYNARD T., MARCELLIN P., BISSERY A., MYERS R.P., MOUSSALLI J., DEGOS F., DHUMEAUX D., RIACHI G., BRONOWICKI J.P., BRISSOT P., BUFFET C., SERFATY L., NAVEAU S., SOGNI P., BEAUGRAND M., GAYNO S., LARREY D., SAMUEL D., EUGENE C., POL S., BEDOSSA P., DAURAT V., CHAUMET-RIFFAUD P.**

Reinforced interferon alpha-2b and ribavirin is more effective than standard combination therapy in the retreatment of chronic hepatitis C previously nonresponsive to interferon: a randomized trial.

*J. Viral Hepat.*, 10 (3), 197-204, 2003

(Services cités : Hépatologie Adulte)

Interferon-alpha (IFN) monotherapy results in sustained virological clearance in a minority of patients with chronic hepatitis C. The aim of this study was to assess the effect of a reinforced regimen combining ribavirin and high-dose IFN for 48 weeks compared with a nonreinforced regimen combining a standard IFN regimen and ribavirin for 24 weeks in nonresponders with chronic hepatitis C. A total of 231 patients with chronic hepatitis C and previous nonresponse to IFN monotherapy were randomized. The reinforced group ( $n = 114$ ) received IFN-2b 6 million units (MU) thrice weekly (TIW) and ribavirin for 48 weeks, and the nonreinforced group ( $n = 117$ ) received IFN-2b 3 MU TIW and ribavirin for 24 weeks. The main outcome measure was a

sustained virological response, defined as negative serum hepatitis C virus (HCV)-RNA 24 weeks following the end of treatment. This endpoint was determined in 98 patients of the reinforced group and 105 patients of the nonreinforced group. At the end of follow-up, a sustained virological response was observed in 29 of the 98 patients (29.6%) in the reinforced group vs 16 of the 105 patients (15.2%) in the nonreinforced group ( $P = 0.014$ ). In multivariate analysis, factors associated with a sustained virological response were treated with a reinforced regimen [odds ratio (OR) 2.9;  $P = 0.06$ ] and genotype 2 or 3 (OR 8.8;  $P < 0.0002$ ). A total of 160 patients had paired biopsies before and after treatment. Histological activity improvement was observed in 32 of 80 patients (40%) and fibrosis worsening in 26 of 80 patients (33%) in the reinforced group vs 13 of 80 (16%) and 19 of 80 (24%) in the nonreinforced group ( $P = 0.30$  and  $0.20$ , respectively). Hence in nonresponders, a high-dose 48-week regimen of IFN and ribavirin combination was more effective than a regimen with interferon at lower dose and ribavirin for 24 weeks only.

**ROSENTHAL E., POIREE M., PRADIER C., PERRONNE C., SALMON-CERON D., GEFFRAY L., MYERS R.P., MORLAT P., PIALOUX G., POL S., CACOUB P.**

Mortality due to hepatitis C-related liver disease in HIV-infected patients in France (Mortavic 2001 study).

*AIDS*, 17 (12), 1803-1809, 2003

(Services cités : Hépatologie Adulte)

**OBJECTIVE** To determine mortality due to end-stage liver disease (ESLD) in a nationwide cohort of HIV-infected patients 5 years after the introduction of highly active antiretroviral therapy (HAART) and to compare this with that observed before and during the early years of HAART. **DESIGN and methods:** All departments of internal medicine and infectious diseases from the GERMIVIC Study Group prospectively recorded all deaths in HIV-infected patients during 2001. Sixty-five departments, following a total of 25 178 HIV-infected patients, participated in the study. Results were compared with those of previous surveys conducted using similar methodology in 1995 and 1997. **RESULTS** Among 265 deaths observed during 2001, 129 (48.7%) were related to AIDS, 38 (14.3%) to ESLD, and 98 (36.7%) to other causes. Mortality due to ESLD represented 28% of non AIDS-related deaths; 36 of the 38 patients (95%) dying from ESLD had chronic hepatitis C virus (HCV) infection. In 2001, deaths due to ESLD (14.3%) were significantly more frequent than in 1995 (1.5%;  $P < 0.01$ ) and 1997 (6.6%;  $P < 0.01$ ). During this interval, the prevalence of hepatocellular carcinoma as a cause of death increased (1995, 4.7%; 1997, 11%; 2001, 25%;  $P < 0.05$ ), as did alcohol consumption ( $P < 0.01$ ). **CONCLUSIONS** In the post-HAART era, ESLD due to HCV is a growing cause of mortality in HIV-infected patients. Increased longevity attributable to HAART, and a higher prevalence of alcohol consumption, are probably involved in this trend.

**VALLET-PICHARD A., REROLLE J.P., FONTAINE H., LAROUSSERIE F., PERALDI M.N., KREIS H., POL S.**

Veno-occlusive disease of the liver in renal transplant patients.

*Nephrol. Dialysis Transplant.*, 18 (8), 1663-1666, 2003

(Services cités : U370, Transplantation & Réanimation Adulte, Hépatologie Adulte, Anatomopathologie)

**VAN NUNEN A.B., HANSEN B.E., SUH D.J., LOHR H.F., CHEMELLO L., FONTAINE H., HEATHCOTE J., SONG B.C., JANSSEN H.L., de MAN R.A., SCHALM S.W.**

Durability of HBeAg seroconversion following antiviral therapy for chronic hepatitis B: relation to type of therapy and pretreatment serum hepatitis B virus DNA and alanine aminotransferase. *Gut*, 52 (3), 420-424, 2003

(Services cités : Hépatologie Adulte)

Background and aims: Interferon (IFN) induced hepatitis B e antigen (HBeAg) seroconversion is durable in 80-90% of chronic hepatitis B patients. Preliminary reports on the durability of HBeAg seroconversion following lamivudine are contradictory. We investigated the durability of response following IFN, lamivudine, or IFN-lamivudine combination therapy in a meta-analysis of individual patient data. PATIENTS AND METHODS: Twenty four centres included 130 patients in total with an HBeAg seroconversion (HBeAg negative, antibodies to hepatitis B e antigen positive) at the end of antiviral therapy: 59 with lamivudine, 49 with interferon, and 22 with combination therapy. Relapse was defined as confirmed reappearance of HBeAg.

RESULTS: The three year cumulative HBeAg relapse rate by the Kaplan-Meier method was 54% for lamivudine, 32% for IFN, and 23% for combination therapy (p=0.01). Cox regression analysis identified pretreatment hepatitis B virus (HBV) DNA, alanine aminotransferase (ALT), sex, and therapy as independent predictive factors of post-treatment relapse; Asian race, previous therapy, centre, and type of study were not predictive of relapse. The relative HBeAg relapse risk of lamivudine compared with IFN therapy was 4.6 and that of combination therapy to IFN therapy 0.7 (p(overall)=0.01). CONCLUSIONS: The durability of HBeAg seroconversion following lamivudine treatment was significantly lower than that following IFN or IFN-lamivudine combination therapy. The risk of relapse after HBeAg seroconversion was also related to pretreatment levels of serum ALT and HBV DNA, but independent of Asian race.

**2002**

**ANDRE P., KOMURIAN-PRADEL F., DEFORGES S., PERRET M., BERLAND J.L., SODOYER M., POL S., BRECHOT C., PARANHOS-BACCALA G., LOTTEAU V.**

Characterization of low- and very-low-density hepatitis C virus RNA-containing particles. *J. Virol.*, 76 (14), 6919-6928, 2002

(Services cités : Hépatologie Adulte)

The presence of hepatitis C virus (HCV) RNA-containing particles in the low-density fractions of plasma has been associated with high infectivity. However, the nature of circulating HCV particles and their association with immunoglobulins or lipoproteins as well as the characterization of cell entry have all been subject to conflicting reports. For a better analysis of HCV RNA-containing particles, we quantified HCV RNA in the low-density fractions of plasma corresponding to the very-low-density lipoprotein (VLDL), intermediate-density lipoprotein, and low-density lipoprotein (LDL) fractions from untreated chronically HCV-infected patients. HCV RNA was always found in at least one of these fractions and represented 8 to 95% of the total plasma HCV RNA. Surprisingly, immunoglobulins G and M were also found in the low-density fractions and could be used to purify the HCV RNA-containing particles (lipo-viro-particles [LVP]). Purified LVP were rich in triglycerides; contained at least apolipoprotein B, HCV RNA, and core protein; and appeared as large spherical particles with a diameter of more than 100 nm and with internal structures. Delipidation of these particles resulted in capsid-like structures recognized by anti-HCV core protein antibody. Purified LVP efficiently bind and enter hepatocyte cell lines, while serum or whole-density fractions do not. Binding of these particles was competed out by VLDL and LDL from noninfected donors and was blocked by anti-apolipoprotein B and E antibodies, whereas upregulation of the LDL receptor increased their internalization. These results suggest that the infectivity of LVP is mediated by endogenous

proteins rather than by viral components providing a mechanism of escape from the humoral immune response.

**FONTAINE H.**

L'hépatite C dans certaines populations de malades : les enfants, les hémophiles et les thalassémiques, les hémodialysés et les transplantés rénaux.

*Gastroentérol. Clin. Biol.*, 26 Spec No 2 B91-B104, 2002

(Services cités : Hépatologie Adulte)

**GURR W., YAVARI R., WEN L., SHAW M., MORA C., CHRISTA L., SHERWIN R.S.**

A Reg Family Protein Is Overexpressed in Islets From a Patient With New-Onset Type 1 Diabetes and Acts as T-Cell Autoantigen in NOD Mice.

*Diabetes*, 51 (2), 339-346, 2002

(Services cités : Hépatologie Adulte)

Genes overexpressed in pancreatic islets of patients with new-onset type 1 diabetes are potential candidates for novel disease-related autoantigens. RT-PCR-based subtractive hybridization was used on islets from a patient who died at the onset of type 1 diabetes, and it identified a type 1 diabetes-related cDNA encoding hepatocarcinoma-intestine-pancreas/pancreatic-associated protein (HIP/PAP). This protein belongs to the family of Reg proteins implicated in islet regeneration; its gene contains a putative interleukin-6 (IL-6) response element. Islets from healthy cadaveric human donors released HIP/PAP protein into the culture medium, and this release was enhanced by the addition of IL-6. The expression pattern of mouse homologues of HIP/PAP was determined in pancreata of prediabetic and diabetic NOD mice. Both groups showed positive immunostaining for HIP/PAP in islets and ductal epithelium. To test whether HIP/PAP is a target of islet-directed autoimmunity, we measured splenic T-cell responses against HIP/PAP in NOD mice. Spontaneous proliferation was detected after 4 weeks. Lymphocytes from islet infiltrates and pancreatic lymph nodes from 7- to 10-week-old NOD mice were used to establish an HIP/PAP-specific I-A(g7)-restricted T-cell line, termed WY1, that also responded to mouse islets. WY1 cells homed to islets of NOD-SCID mice and adoptively transferred disease when coinjected with purified CD8(+) cells from diabetic NOD mice. Our conclusion was that differential cloning of Reg from islets of a type 1 diabetic patient and the response of Reg to the cytokine IL-6 suggests that HIP/PAP becomes overexpressed in human diabetic islets because of the local inflammatory response. HIP/PAP acts as a T-cell autoantigen in NOD mice. Therefore, autoimmunity to HIP/PAP might create a vicious cycle, accelerating the immune process leading to diabetes.

**HALFON P., POL S., BOURLIERE M., CACOUB P.**

Hepatitis B virus genotypes: clinical, epidemiological and therapeutic implications.

*Gastroentérol. Clin. Biol.*, 26 (11), 1005-1012, 2002

(Services cités : Hépatologie Adulte)

**HERMINE O., LEFRERE F., BRNOWICKI J.P., MARIETTE X., JONDEAU K., ECLACHE-SAUDREAU V., DELMAS B., VALENSI F., CACOUB P., BRECHOT C., VARET B., TROUSSARD X.**

Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection.

*N. Engl. J. Med.*, 347 (2), 89-94, 2002

(Services cités : Hématologie Adulte, Hépatologie Adulte, FRE 2444)

**BACKGROUND:** Some epidemiologic studies suggest a link between hepatitis C virus (HCV) infection and some B-cell non-Hodgkin's lymphomas. We undertook this study after a patient with splenic lymphoma with villous lymphocytes had a hematologic response after antiviral treatment of HCV infection. **METHODS:** Nine patients who had splenic lymphoma with villous lymphocytes and HCV infection were treated with interferon alfa-2b (3 million IU three times per week) alone or in combination with ribavirin (1000 to 1200 mg per day). The outcomes were compared with those of six similarly treated patients with splenic lymphoma with villous lymphocytes who tested negative for HCV infection. **RESULTS:** Of the nine patients with HCV infection who received interferon alfa, seven had a complete remission after the loss of detectable HCV RNA. The other two patients had a partial and a complete remission after the addition of ribavirin and the loss of detectable HCV RNA. One patient had a relapse when the HCV RNA load again became detectable in blood. In contrast, none of the six HCV-negative patients had a response to interferon therapy. **CONCLUSIONS:** In patients with splenic lymphoma with villous lymphocytes who are infected with HCV, treatment with interferon can lead to regression of the lymphoma.

**HUE S., CACOUB P., RENO C., HALFON P., THIBAUT V., CHARLOTTE F., PICON M., RIFFLET H., PIETTE J.C., POL S., CAILLAT-ZUCMAN S.**

Human leukocyte antigen class II alleles may contribute to the severity of hepatitis C virus-related liver disease.

*J. Infect. Dis.*, 186 (1), 106-109, 2002

(Services cités : Hépatologie Adulte, Laboratoire d'Immunologie)

Whether the host's immune response genes influence the severity of hepatitis C virus (HCV) liver disease is controversial. Human leukocyte antigen (HLA) class II alleles were analyzed in 233 HCV RNA-positive patients with chronic active hepatitis (197 patients with Knodell index of fibrosis F0-F3 and 36 patients with index of F4). The 2 groups did not differ by sex, duration of infection, mode of contamination, alcohol consumption, or HCV genotype. Patients with cirrhosis were older than those without (56 +/- 12 vs. 46 +/- 14 years;  $P < 10^{-4}$ ) and had a lower DRB1\*11 allele frequency (5.6% vs. 14.5%;  $P = .037$ ), whereas DRB1\*03 and DQB1\*0201 frequencies appeared to be higher (DRB1\*03, 18.1% vs. 9.6%; DQB1\*0201, 37.5% vs. 23.4%;  $P = .04$ , corrected  $P$  value is not significant). Mean index of fibrosis was higher in DR3-positive than in DR11-positive patients (2.14 vs. 1.58;  $P = .05$ ). By multivariate analysis, cirrhosis was associated with male sex and age  $\geq 50$  years. HLA class II alleles may weakly contribute to the severity of HCV liver disease. Of persons infected with HCV, only 15%-20% spontaneously clear the virus, and the rest become chronically infected.

**LE NAOUR F., BRICHORY F., MISEK D.E., BRECHOT C., HANASH S.M., BERETTA L.**

A distinct repertoire of autoantibodies in hepatocellular carcinoma identified by proteomic analysis.

*Mol. Cell. Proteomics*, 1 (3), 197-203, 2002

(Services cités : Hépatologie Adulte)

Chronic infections with hepatitis B (HBV) and hepatitis C (HCV) viruses are major risk factors for hepatocellular carcinoma (HCC). We have utilized a proteomic approach to determine whether a distinct repertoire of autoantibodies can be identified in HCC. Sera from 37 patients with HCC and 31 subjects chronically infected with HBV or HCV without HCC were

investigated. Sera from 116 patients with other cancers, three patients with systemic lupus erythematosus, and 24 healthy subjects were utilized as controls. We report the identification of eight proteins, for each of which autoantibodies were detected in sera from more than 10% of patients with HCC but not in sera from healthy individuals ( $p < 0.05$ ). Autoantibodies to four of these proteins were detected at a comparable frequency in sera from patients with chronic hepatitis. The other four proteins, which consisted of calreticulin isoforms, cytokeratin 8, nucleoside diphosphate kinase A, and F(1)-ATP synthase beta-subunit, induced autoantibodies among patients with HCC, independently of their HBV/HCV status. Calreticulin, and a novel truncated form of calreticulin (Crt32) we have identified, most commonly elicited autoantibodies among patients with HCC (27%). We conclude that a distinct repertoire of autoantibodies is associated with HCC that may have utility in early diagnosis of HCC among high risk subjects with chronic hepatitis.

**LEBRAY P., BENHAMOU Y., POL S., MYERS R.P., POYNARD T., DI MARTINO V.**  
NNRTI-related or -unrelated hepatotoxicity?  
*Hepatology*, 36 (2), 512-513, 2002  
(Services cités : Hépatologie Adulte, U370)

**PELLETIER S., VAUCHER E., AIDER R., MARTIN S., PERNEY P., BALMES J.L., NALPAS B.**  
Wine consumption is not associated with a decreased risk of alcoholic cirrhosis in heavy drinkers.  
*Alcohol Alcohol.*, 37 (6), 618-621, 2002  
(Services cités : Hépatologie Adulte)  
- AIMS: While it was thought that all alcoholic beverages share a similar liver toxicity when drunk at a high level, recent epidemiological surveys have suggested that wine drinking might decrease the risk of alcoholic cirrhosis in heavy drinkers. Therefore, we performed a study aiming to analyse the type and the intake levels of alcoholic beverages in heavy drinkers according to the severity of the liver disease. METHODS: This is a case-control study enrolling 42 cirrhotic and 60 non-cirrhotic patients. Liver status was assessed using clinical, biological, histological and ultrasonographic procedures. Alcohol consumption was recorded using the Lifetime Drinking History method. RESULTS: We did not find any significant differences in total alcohol consumption between cases and controls and, moreover, in our series, the relative percentage of pure alcohol drunk in wine was significantly higher in cirrhotic, than in non-cirrhotic, patients. CONCLUSIONS: Our results confirm that the absence of a link between the type of alcoholic beverage and the occurrence of cirrhosis is still valid.

**POL S.**  
Traitement de l'hépatite chronique C chez les malades ayant une co-infection VIH: efficacité et tolérance.  
*Gastroentérol. Clin. Biol.*, 26 Spec No 2 B264-B273, 2002  
(Services cités : Hépatologie Adulte, U370)

**POL S.**  
Co-infection HIV/HBV.  
*Gastroentérol. Clin. Biol.*, 26 (5), 518-521, 2002  
(Services cités : Hépatologie Adulte)

**POL S., VALLET-PICHARD A., FONTAINE F.**

Hepatitis c and human immune deficiency coinfection at the era of highly active antiretroviral therapy.

*J. Viral Hepatitis*, 9 (1), 1-8, 2002

(Services cités : Hépatologie Adulte, U370)

Interactions between human immunodeficiency virus (HIV) and hepatitis C virus (HCV) have been widely studied before the introduction of highly active antiretroviral therapies (HAART). We reviewed the potential impact of HAART on hepatitis C as well as the interactions between HIV and HCV therapies. Physicians should be aware of the potential risk of: (i) symptomatic liver disease in HCV-HIV-coinfected patients at the era of triple antiretroviral therapy; (ii) potential liver deterioration paralleling immune restoration; (iii) lack of impact of triple antiretroviral therapy on HCV load; and (iv) potential drug-related hepatitis which may modify the natural history of HCV-related liver disease. Liver biopsies should be performed regularly in these patients in order to identify patients with severe liver disease who require early initiation of anti-HCV therapy under close monitoring of their immune status. Treatment is, to date, based on the combination of ribavirin and interferon with an expected sustained response rate around 25%. An important unresolved issue is to better delineate the temporal place of anti-HCV and anti-HIV antiviral therapies. At least in coinfecting patients with significant liver disease, namely necro-inflammatory activity and/or fibrosis [greater-than-or-equal] 2, we believe that anti-HCV therapy is the priority since it lessens the risk of drug-induced hepatitis and of hepatitis due to immune restoration.

**POL S., LEBRAY P.**

N-acetylcysteine for paracetamol poisoning : effect on prothrombin.

*Lancet*, 360 (9340), 1115, 2002

(Services cités : Hépatologie Adulte, U370)

**POL S., VALLET-PICHARD A., FONTAINE H., LEBRAY P.**

HCV infection and hemodialysis.

*Semin. Nephrol.*, 22 (4), 331-339, 2002

(Services cités : Hépatologie Adulte, U370)

Hepatitis C virus (HCV) infections are frequent in hemodialyzed patients and are mainly related to transfusions and nosocomial contamination. HCV-related infection may result in cirrhosis in 10% of dialysis patients and is worsened by transplantation because of the immunosuppressive therapy for prevention of graft rejection. Because there is a risk for significant liver disease and because cirrhosis contraindicates a renal transplantation, a liver biopsy should be performed early in HCV-RNA positive hemodialysis patients to evaluate histologic impact of the liver disease. A combined liver-kidney transplantation should be discussed in dialysis patients with cirrhosis. Standard alpha-interferon is the only treatment for HCV in dialysis patients because ribavirin is contraindicated by a high risk for hemolytic anemia. It leads to an overall 30% rate of sustained viral eradication. It is indicated in dialysis patients with acute hepatitis C, significant liver disease (fibrosis score  $\geq 2$ ), or symptomatic cryoglobulinemia, and to candidates for renal transplantation, whatever the severity of the liver disease. Indeed, alpha-interferon is contraindicated in kidney recipients given the risk for rejection. Preventive treatment for HCV is only respect for universal hygiene rules in the dialysis setting because there is no available vaccine. Copyright 2002, Elsevier Science (USA). All rights reserved.

**RENOU C., POL S., HALFON P., CAILLAT-ZUCMAN S.**

Controversies about the histological features of chronic HCV patients with persistently normal alanine transaminase levels: what can be done about the present definition?

*Gastroenterology*, 123 (5), 1748-1749, 2002

(Services cités : Hépatologie Adulte, Laboratoire d'Immunologie)

**RENOU C., HALFON P., POL S., CACOUB P., JOUVE E., BRONOWICKI J.P., ARPURT J.P., RIFFLET H., PICON M., CAUSSE X., CANVA V., DENIS J., TRAN A., BOURLIERE M., OUZAN D., PARIENTE A., DANTIN S., ALRIC L., CARTIER V., REVILLE M., CAILLAT-ZUCMAN S.**

Histological features and HLA class II alleles in hepatitis C virus chronically infected patients with persistently normal alanine aminotransferase levels.

*Gut*, 51 (4), 585-590, 2002

(Services cités : Hépatologie Adulte, Laboratoire d'Immunologie)

**OBJECTIVE:** A significant proportion of individuals with chronic hepatitis C virus (HCV) infection have persistently normal alanine aminotransferase (ALT) levels. Although data are controversial, such patients usually have weaker histological damage and a lower progression rate of fibrosis. The aims of this study were: (1) to compare demographic, virological, and histological parameters of HCV patients with normal ALT values with those of HCV patients with elevated ALT levels; and (2) to determine whether HLA class II alleles contribute to the persistence of normal ALT levels in HCV patients. **PATIENTS AND METHODS:** Eighty three patients with chronic HCV infection and persistently normal ALT values (group 1) and 233 patients with chronic HCV infection and elevated ALT levels (group 2) were studied.

Histological features were expressed using Knodell and Metavir scores. HLA DRB1\* and DQB1\* genotyping was performed using hybridisation with sequence specific oligonucleotides after genomic amplification. The kappa2 and Fisher's exact tests were used to compare discrete variables and phenotype frequencies between the two groups, and Wilcoxon's test was used for continuous variables. A multivariate logistic regression model was used to determine which variables predicted normal ALT values. **RESULTS:** ALT levels were correlated with the severity of liver damage. In group 1, 93% of patients had an F0 or F1 Metavir index of fibrosis compared with 47% of patients in group 2 ( $p < 0.001$ ). A longer duration of infection ( $p < 0.001$ ) and increased DRB1\*11 phenotype frequency ( $p = 0.03$ ) were observed among patients with normal ALT. The two groups did not differ with regard to the mode of contamination or viral genotype. After logistic regression, young age ( $p = 0.0008$ ), female sex ( $p = 0.01$ ), long duration of infection ( $p = 0.0001$ ), and HLA DRB1\*11 ( $p = 0.050$ ) were more strongly associated with persistence of normal ALT. **CONCLUSIONS:** Our study confirms that patients with chronic hepatitis C and normal ALT levels have less severe liver disease than those with elevated ALT levels. This particular biochemical outcome may be explained, at least in part, by host immunogenetic factors such as the presence of HLA-DRB1\*11.

**SA CUNHA A., BONTE E., DUBOIS S., CHRETIEN Y., ERAISER T., DEGOTT C., BRECHOT C., TRAN P.L.**

Inhibition of rat hepatocellular carcinoma tumor growth after multiple infusions of recombinant Ad.AFPtk followed by ganciclovir treatment.

*J. Hepatol.*, 37 (2), 222-230, 2002

(Services cités : Hépatologie Adulte)

**BACKGROUND/AIMS:** The antitumor efficiency of thymidine kinase (tk) in Herpes Simplex

virus-tk-based gene therapy of rat hepatocellular carcinoma (HCC) was examined by specific transcriptional targeting of tk to tumor cells by the alpha-fetoprotein (AFP) gene promoter and by multiple infusions of recombinant adenovirus Ad.AFPtk. METHODS: We developed a surgical procedure that allows efficient, non-invasive delivery (during 2 months) of recombinant Ad via the intra-hepatic artery (IHA) route. RESULTS: Treatment of tumor-bearing rats with either three or five doses of  $5 \times 10^9$  pfu Ad.AFPtk, administered every 3 days, and followed by intra-peritoneal treatment with ganciclovir (GCV), resulted in tumor growth inhibition and apoptosis, when compared to untreated tumor-bearing rats or animals treated with Ad.AFPlacZ or buffered saline. No treatment-related toxicity was noted. Antitumor efficacy, based on tumor size and number of tumors, was demonstrated in more than 50% of Ad.AFPtk-treated rats, as compared to control rats ( $P < 0.0005$ ). CONCLUSIONS: Our results demonstrate the safety and potential of multiple Ad.AFPtk administrations by the IHA route to inhibit HCC tumor growth, and support further clinical investigation of Ad.AFPtk gene therapy for treatment of multifocal tumor lesions in most primary liver cancers.

**SIMONETTA-MOREAU M., MEUNIER S., VIDAILHET M., POL S., GALITZKY M., RASCOL O.**

Transmission of group II heteronymous pathways is enhanced in rigid lower limb of de novo patients with Parkinson's disease.

*Brain*, 125 (Pt 9), 2125-2133, 2002

(Services cités : Hépatologie Adulte)

A potent heteronymous excitation of quadriceps motoneurons via common peroneal group II afferents has recently been demonstrated in normal subjects. The aim of this study was to investigate whether this group II excitation contributes to rigidity in Parkinson's disease. The early and late facilitations of the quadriceps H reflex elicited by a conditioning volley to the common peroneal nerve (CPN) at twice motor threshold, attributed to non-monosynaptic group I and group II excitations, respectively, were investigated. The comparison was drawn between results obtained in 20 "de novo" patients with Parkinson's disease (hemiparkinsonian, 17; bilateral, three) and 20 age-matched normal subjects. There was no statistically significant effect of "group" (patients/controls), "duration", "global severity" [Unified Parkinson's Disease Rating Scale (UPDRS)] or "side" (unilaterally versus bilaterally affected) factors on either group I or group II facilitations. To further the analysis, the factors of status (affected or non-affected limb), akinesia (lower limb akinesia score) and rigidity (lower limb rigidity score) were entered in a general linear model to explain the variations of the quadriceps H reflex facilitation. Rigidity was the only factor useful in predicting the value of the group II facilitation of the quadriceps H reflex ( $P < 0.007$ ). Group I and group II facilitation was then compared between the rigid, non-rigid and control lower limbs [multivariate analysis of variance (MANOVA)]. Results are represented as mean SEM (standard error of the mean). Group II facilitation was enhanced in the rigid lower limb of unilaterally affected patients (153.2 7% of control H reflex) compared with non-rigid lower limbs (124 4% of control H reflex;  $P < 0.007$ ) or control lower limbs (126.1 4.1%;  $P < 0.01$ ). There was no difference between the non-rigid lower limbs of the unilaterally affected patients and the control lower limbs, but a difference was observed between the rigid lower limbs of unilaterally less affected and bilaterally more affected patients (153.2 7% and 123.8 7.5% of control H reflex, respectively;  $P < 0.04$ ). These results suggest a facilitation of the transmission in the interneuronal pathway activated by group II afferents in rigid lower limb of de novo hemiparkinsonian patients, probably resulting from a change in their descending monoaminergic inhibitory control.

**VALLET-PICHARD A., FONTAINE H., POL S.**

Atheroma and hepatitis C virus.

*Gastroentérol. Clin. Biol.*, 26 (11), 989-890, 2002

(Services cités : Hépatologie Adulte, U370)

**VALLET-PICHARD A., POL S.**

Hépatites virales. Anomalies biologiques hépatiques chez un sujet asymptomatique.

*Rev. Prat.*, 52 (14), 1605-1617, 2002

(Services cités : Hépatologie Adulte)

**ZYLBERBERG H., NALPAS B., CARNOT F., SKHIRI H., FONTAINE H., LEGENDRE C., KREIS H., BRECHOT C., POL S.**

Severe evolution of chronic hepatitis c in renal transplantation: a case control study.

*Nephrol. Dial. Transplant.*, 17 (1), 129-133, 2002

(Services cités : Hépatologie Adulte, Transplantation & Réanimation Adulte)

Background. To evaluate the impact of kidney transplantation on histopathological progression of hepatitis C virus (HCV)-related liver disease, Methods. In a retrospective study, 28 HCV-positive renal transplant patients, who underwent two sequential liver biopsies with a mean of 7.1 +/- 4.0 years, were compared with 28 matched immunocompetent controls. Results. According to the Metavir score, the initial and final activity scores (from 0 to 3) increased from 0.2 +/- 0.4 to 1.4 +/- 1.1 (P<0.001) and those of fibrosis (from 0 to 4) from 0.5 +/- 0.5 to 2.0 +/- 1.4 (P < 0.001) in the transplanted group, respectively, whereas the respective differences were not significant in the control group. The yearly progression rate of activity and fibrosis was significantly higher in the renal transplant group as compared with the immunocompetent group: 0.26 +/- 0.41 vs 0.01 +/- 0.19 (P<0.01) and 0.26 +/- 0.35 vs 0.05 +/- 0.21 (P<0.03), respectively. Twenty (71.5%) and 14 (50.0%) of the renal allograft recipients had activity and fibrosis progression as compared with four (16%) (P<0.001) and four (16%) (P<0.01) in immunocompetent patients; six kidney recipients (21.4%) evolved to cirrhosis vs only one in the control group (3.6%) (P = 0.07). Liver-related mortality was significantly higher during the follow-up period in renal transplant patients than in the control group (10 vs 0%) (P<0.05). Conclusion. Using conventional immunosuppressive regimen, renal transplantation is associated with a more severe evolution of chronic hepatitis C as compared with HCV-infected immunocompetent subjects. Thus, the histopathological evaluation should be performed and anti-viral therapy discussed before renal transplantation. [References: 33]

**2001**

**BRECHOT C., THIERS V., KREMSDORF D., NALPAS B., POL S., PATERLINI-BRECHOT P.**

Persistent hepatitis b virus infection in subjects without hepatitis b surface antigen: clinically significant or purely "occult"?

*Hepatology*, 34 (1), 194-203, 2001

(Services cités : Hépatologie Adulte, U370)

**DEGOS F., POL S., CHAIX M.L., LAFFITTE V., BUFFET C., BERNARD P.H., DEGOTT C., CARNOT F., RIFFAUD P.C., CHEVRET S.**

The tolerance and efficacy of interferon-alpha in haemodialysis patients with hcv infection: a

multicentre, prospective study.

*Nephrol. Dialysis Transplant.*, 16 (5), 1017-1023, 2001

(Services cités : Hépatologie Adulte, Laboratoire de Microbiologie)

Background. A prospective multicentre study was initiated in HCV-infected haemodialysis patients to assess the tolerance and efficacy of alpha -2b interferon. Methods. We had planned to include 120 patients with HCV RNA detectable by polymerase chain reaction (PCR) (Amplicor Roche) and histologically documented chronic hepatitis. The dose of alpha -interferon was 3 million units (MU) three times weekly (TTW) to be reduced to 1.5 MU TTW in case of side-effects. Tolerance was evaluated monthly; virological efficacy was evaluated by PCR. A liver biopsy was performed at month 18 (M18). Results. (a) Tolerance. After 37 patients had been included, the study was discontinued by the promoting institution because of severe side-effects requiring that treatment be stopped in 19 patients. The side-effects were: cardiac (4) neuropsychiatric (2), digestive (3), acute necrosis of the graft (1), severe asthenia (9), minor side-effects were observed in 22 patients. A complete 12-month course was completed in 12 patients for the 3 MW TTW dose and in six patients for the 1.5 MU TTW reduced dose. Normal ALT level (OR, 0.16; CI 95%, 0.03-0.89) at inclusion was associated with interruption of treatment (univariate analysis). (b) Efficacy. Sustained virological response was observed in only seven (18.9%), of the 18 patients who completed the treatment (38%). Increased ALT at inclusion (OR, 1.04; CI 95%, 1.01-1.09) and cumulated doses of interferon (OR, 1.01, CI 95% 1.004-1.026) were jointly associated with a sustained response, while positive PCR at M2 was strongly predictive of treatment failure. Conclusion: Tolerance of interferon is poor in haemodialysis patients. Sustained response is fairly high in patients who have 12 months of treatment and seems to be based on the immune status of the patients (ALT) and the cumulative doses of interferon. [References: 19]

**DESENCLOS J.C., BOURDIOL-RAZES M., ROLIN B., GARANDEAU P., DUCOS J., BRECHOT C., THIERS V.**

Hepatitis C in a ward for cystic fibrosis and diabetic patients: possible transmission by spring-loaded finger-stick devices for self-monitoring of capillary blood glucose.

*Infect. Control. Hosp. Epidemiol.*, 22 (11), 701-707, 2001

(Services cités : Hépatologie Adulte)

OBJECTIVE: To identify the routes of transmission in a nosocomial outbreak of hepatitis C virus (HCV) infection. DESIGN: Epidemiological investigation, including screening for HCV of hospitalized patients, and a retrospective cohort study, review of hygiene and medical practices, and molecular comparison of HCV isolates. SETTING: A specialized care unit for cystic fibrosis (CF) and diabetic patients at an acute-care facility in the south of France. RESULTS: Of the 57 CF patients (age in 1995: 2-28 years), 38 (66.7%) were tested and 22 (57.9%) were anti-HCV positive. Eight (50%) of 16 patients with anti-HCV antibody tested by polymerase chain reaction were viremic. No patients had received blood products or had any history of intravenous drug use. All 18 (100%) patients with CF who had ever undergone self-monitoring of capillary blood glucose in the unit were anti-HCV positive, compared to 4 (20%) of 20 who had not (relative risk, 5.0; 95% confidence interval, 2.1-12.0). Seventy (39.5%) of the patients with diabetes were screened for anti-HCV; 12 (18.8%) tested positive, with 3 (25%) positive for HCV-RNA. Patients with diabetes had routine capillary blood glucose monitoring while hospitalized and shared with CF patients the same spring-triggered devices for capillary blood glucose monitoring. The disposable platform of the devices was not changed between patient use. All HCV isolates belonged to the type 1, subtype b, and phylogenetic analysis showed a close homology by

sequencing of NS5b and E2/HVR regions. CONCLUSION: As reported earlier for the hepatitis B virus, shared spring-triggered devices for capillary blood glucose monitoring by finger puncture may transmit HCV. Strict application of Standard Precautions procedures is warranted in any healthcare setting.

**FONTAINE H., NALPAS B., POULET B., CARNOT F., ZYLBERBERG H., BRECHOT C., POL S.**

Hepatitis activity index is a key factor in determining the natural history of chronic hepatitis C. *Hum. Pathol.*, 32 (9), 904-909, 2001

(Services cités : Hépatologie Adulte, U370)

To analyze the spontaneous pathologic progression of chronic hepatitis C, we analyzed the histopathologic semiquantitative scores (Metavir and Knodell) of sequential liver biopsies performed in untreated hepatitis C virus (HCV)-infected patients. Subjects included 35 men and 41 women, with a mean age of 41 +/- 12 years, a duration of HGV infection of 11 +/- 5 years, and an interval between liver biopsies of 3.7 +/- 2.5 years. Results obtained using the Knodell score and the Metavir score were similar. At the first biopsy, 78.9% of patients had a low activity score (AO-A1) and 82.9% had a low fibrosis score (F0-F2). At the second biopsy, the activity decreased in 9.2%, was unchanged in 72.4%, and increased in 18.5%. An increase in activity was more frequently observed in patients infected with genotype I (28.9%) than with others (7.7%; P =.04); the yearly progression of activity was significantly higher in patients with a low rather than high initial activity score (0.11 v -0.02; P <.01). An increase in fibrosis was noted in 13.3% of those with a low and 43.8% of those with a high initial activity score (P <.01), with a highest rate of yearly fibrosis progression (0.12 U). In multivariate analysis, only a high activity score was significantly associated with an increased risk of fibrosis progression (relative risk, 25.5; 95% confidence interval, 2.7 to 238; P =.004). Spontaneous chronic hepatitis C evolution is worsening in only 20% of patients. Fibrosis progression is significantly associated with the necroinflammatory activity suggesting that this factor should be regarded as a major clue for deciding therapy. Copyright (C) 2001 by W.B. Saunders Company [References: 33]

**FONTAINE H., NALPAS B., CARNOT F., BRECHOT B., POL S.**

Effect of pregnancy on chronic hepatitis c - reply.

*Lancet*, 357 (9253), 389-390, 2001

(Services cités : Hépatologie Adulte, U370)

**FONTAINE H., POL S.**

Prevention and treatment of viral hepatitis in renal failure.

*Néphrologie*, 22 (7), 339-347, 2001

(Services cités : Hépatologie Adulte)

Viral hepatotropic infections may lead to diagnostic and therapeutic problems in hemodialysis patients and kidney recipients. The parenteral and community-acquired routes of contamination of hepatitis B and C viruses explain their high frequency in this population. Their impact because the immunosuppressive treatments, is harmful with a decrease in patients and allografts survival; cirrhosis is a contra-indication for renal transplantation since associated with a bad short-term prognosis and may require a combined kidney-liver transplantation. Thus, a liver biopsy is recommended in order to evaluate the histopathological severity of the liver disease (stage and grade) and to precise if an antiviral treatment appears necessary, especially because interferon-a, the main treatment of hepatitis B and C infections, is contra-indicated in kidney recipients

because of the risk of graft rejection. In summary, the diagnosis of viral hepatotropic infections has to be early undergone and its pathological impact has to be evaluated by a liver biopsy. The best treatment has to be prophylactic (vaccination against hepatitis B virus and the respect of universal hygiene rules for hepatitis C virus). [References: 106]

**FONTAINE H., POL S.**

Side effects of interferon-alpha in treating hepatitis c virus infection.

*Transplant. Proc.*, 33 (3), 2327-2329, 2001

(Services cités : Hépatologie Adulte, U370)

**GAGNADOUX M.F., LACAÏLLE F., NIAUDET P., REVILLON Y., JOUVET P., JAN D., GUEST G., CHARBIT M., BROYER M.**

Long term results of liver-kidney transplantation in children with primary hyperoxaluria.

*Pediat. Nephrol.*, 16 (12), 946-950, 2001

(Services cités : Hépatologie Adulte, Néphrologie Pédiatrique, Chirurgie Pédiatrique, Réanimation Pédiatrique)

From 1990 to 2000, we performed eight liver-kidney transplants in eight children, aged 1-16 years, with end-stage renal failure (ESRF) due to primary hyperoxaluria (PHI). The duration of dialysis before transplantation ranged from 2 to 42 months (mean 14 months) and was <1 year in four patients. Only the first patient underwent postoperative hemodialysis; in the other five, we chose to induce maximal diuresis from the first hours with intravenous and intragastric hyperhydration (greater than or equal to 3 l/m<sup>2</sup>) per day). High water intake with nocturnal tube hydration was maintained for 6 months to 5 years, as long as oxaluria exceeded 0.5 mmol/day. A quadruple sequential immunosuppressive regimen was used. Two patients died during liver graft surgery. The other six patients are alive and well, with a mean follow-up of 7.4 years (range 5-11 years). Patient and graft survival is 75% at 5 years. At latest follow-up, liver tests were normal in all six patients; creatinine clearance ranged from 55 to 95 ml/min per 1.73 m<sup>2</sup> (mean=74). Oxaluria was lower than 0.4 mmol/day in all patients (mean=0.22). The six patients underwent 15 renal biopsies, 1-11 years after transplantation. Chronic transplant nephropathy was present in four patients and mild cyclosporin nephrotoxicity in another. No oxalate crystals were seen and repeat ultrasonography has been consistently normal in all patients. The three patients with bone oxalosis showed progressive complete healing of bone lesions. All six children or adolescents now live a normal life. From this series, we conclude that early combined liver-kidney transplantation is the treatment of choice for children with ESRF due to primary hyperoxaluria. [References: 16]

**HUO T.I., WANG X.W., FORGUES M., WU C.G., SPILLARE E.A., GIANNINI C., BRECHOT C., HARRIS C.C.**

Hepatitis b virus x mutants derived from human hepatocellular carcinoma retain the ability to abrogate p53-induced apoptosis.

*Oncogene*, 20 (28), 3620-3628, 2001

(Services cités : Hépatologie Adulte)

Chronic hepatitis B virus (HBV) infection and the integration of its X gene (HBx) are closely associated with the development of hepatocellular carcinoma (HCC). The integrated HBx frequently is truncated or contains point mutations. Previous studies indicated that these HBx mutants have a diminished co-transactivational activity. We have compared the effects of wildtype (wt) HBx and its naturally occurring mutants derived from human HCCs on

transcriptional co-transactivation, apoptosis and interactive effects with p53. We demonstrated that overexpression of mutant, but not wt HBx, is defective in transcriptional co-transactivation of the NF-kappaB-driven luciferase reporter. By using a microinjection technique, the HBx mutants were shown to have an attenuated pro-apoptotic activity. This deficiency may be attributed to multiple mutations in the co-transactivation domain of HBx, that leads to decreased stability of the translated product. However, wt or mutant HBx bind to p53 in vitro and retain their ability to block p53-mediated apoptosis in vivo, which has been implicated as its major tumor suppressor function. The abrogation of p53-mediated apoptosis by integrated HBx mutants may provide a selective clonal advantage for preneoplastic or neoplastic hepatocytes and contribute to hepatocellular carcinogenesis. [References: 92]

**MICHEL M.L., POL S., BRECHOT C., TIOLLAIS P.**

Immunotherapy of chronic hepatitis b by anti hbv vaccine: from present to future.

*Vaccine*, 19 (17-19 Special Issue SI), 2395-2399, 2001

(Services cités : Hépatologie Adulte, U370)

Chronic liver disease and hepatocellular carcinoma associated with chronic hepatitis B virus (HBV)-infection are among the most serious human health problems in highly endemic regions. Current therapeutic approaches to control chronic hepatitis such as interferon-alpha and lamivudine are unsatisfactory. Vaccination would be the therapeutic procedure with the lowest cost and the potentially greatest benefit. The immunogenicity of selected HBV envelope- or capsid-based vaccine formulations for the induction or the broadening of T and B cell responses, deficient in HBV chronic carriers, are currently under study in animal models and in clinical trials. (C) 2001 Elsevier Science Ltd. All rights reserved. [References: 30]

**NALPAS B., MARTIN S., FONTAINE H., FABBRO-PERAY P., BRECHOT C., POL S.**

Impact of medical recommendations on alcohol consumption in hcv positive patients.

*J. Hepatol.*, 35 (2), 312-313, 2001

(Services cités : Hépatologie Adulte, U370)

**NAVEAU S., GIRAUD V., GANNE N., PERNEY P., HASTIER P., ROBIN E., PESSIONE F., CHOSSEGROS P., LAHMEK P., FONTAINE H., RIBARD D., DAO T., FILOCHE B., EL JAMMAL G., SEYRIG J.A., DRAMARD J.M., CHOUSTERMAN M., PILLEGAND B.**

Patients with alcoholic liver disease hospitalized in hepatogastroenterology. a french national multicenter investigation.

*Gastroentérol. Clin. Biol.*, 25 (2), 131-136, 2001

(Services cités : Hépatologie Adulte)

Objectives - To describe the characteristics of in-patients with alcoholic liver disease in Hepatogastroenterology and to evaluate whether geographic location was a risk Factor for cirrhosis. Methods - A French, national, multicenter, prospective investigation was performed in the last quarter of 1997. To be included in the study, patients had to have drunk at least 50 g of alcohol per day for the past year or to have cirrhosis. Results - Seventeen centers included 802 patients 20% had histologically proven cirrhosis or probable cirrhosis. Thirty-five percent had undergone liver biopsy. Twenty Five percent of these patients had cirrhosis without acute alcoholic hepatitis and 37% had cirrhosis with acute alcoholic hepatitis. After dividing France along a Bordeaux-Strasbourg axis, there was more histologically proven or probable cirrhosis in the North (46%) than in the South (36%) (P < 0.005) while daily alcohol intake was greater the

South (150 +/- 6 g) than in the North (129 +/- 4 g) (P < 0.0001). When the six variables (age, sex, daily consumption of alcohol over the past 5 years, presence of hepatitis B surface antigen and antibodies to hepatitis C virus, total duration of alcohol abuse) were considered together in stepwise logistic regression analysis, geographic location changed the prediction of cirrhosis. The odds ratio for cirrhosis in patients living to the North of the Bordeaux-Strasbourg axis was 1.9 (95% confidence interval range 1.1-3.2) (P < 0.02), suggesting the role of nutritional factors. [References: 28]

**POL S.**

Hepatitis c virus and human immunodeficiency virus co-infection.

*Gastroentérol. Clin. Biol.*, 25 (4 Suppl S), B152-B156, 2001

(Services cités : Hépatologie Adulte)

**POL S., FONTAINE H., VALLET-PICHARD A.**

Treatments for hepatitis virus c infections.

*Gastroentérol. Clin. Biol.*, 25 (3), 287-307, 2001

(Services cités : Hépatologie Adulte, U370)

**POL S., NALPAS B., DRISS F., MICHEL M.L., TIOLLAIS P., DENIS J., BRECHOT C.**

Efficacy and limitations of a specific immunotherapy in chronic hepatitis B.

*J. Hepatol.*, 34 (6), 917-921, 2001

(Services cités : Hépatologie Adulte, U370)

Background/Aims: This controlled study aimed to evaluate the efficacy and potential side effects of hepatitis B virus (HBV) vaccination as active immunotherapy in HBV-related chronic hepatitis. Methods: The 118 included patients were 'naive' subjects who had never received any previous anti-HBV therapy, showed detectable serum HBV DNA and had biopsy-proven chronic hepatitis. In a 12-month follow-up they were given either five intramuscular injections of 20 mug of a preS2/S (GenHevac B (R), Pasteur-Merieux) (n = 46) or an S vaccine (Recombivax (R) Merck. & Co.) (n = 34) or no treatment as a control (n = 37). The efficacy of vaccination was evaluated by testing for serum HBV DNA negativation using a standard liquid hybridization assay. Results: Three months after the first three vaccine injections, the percentage of serum HBV DNA negativation was higher in the vaccine groups (16.3%) than in the control group (2.7%) (P = 0.033, by the chi (2) Pearson test) and was more frequently observed in patients who had pretreatment viremia > 200 pg/ml (none in the control group vs. 16.7% in the vaccinated groups) (P = 0.025). After 12 months follow-up and five vaccine injections, there was no difference in the rate of serum HBV DNA negativation between vaccinated and unvaccinated subjects but HBV vaccines significantly decreased the HBV viral load between the sixth and twelfth months (P = 0.04) in contrast with the control group. The rate of HBe/anti-HBe seroconversion after 6 months of follow-up occurred only in eight (13.3%) vaccinated patients and in one (3.6%) of the controls. Disappearance of serum HBsAg was not observed in any of the patients. Conclusions: This controlled study offers direct evidence that the HBV vaccine may decrease HBV replication in chronic hepatitis B patients. It also emphasizes the need for reinforced immunization strategies as well as combination therapies. (C) 2001 European Association for the Study of the Liver. Published by Elsevier Science B.V. All rights reserved. [References: 21]

**POL S.**

Hbv and hcv infections in nephrology.  
*Néphrologie*, 22 (6), 321-322, 2001  
(Services cités : Hépatologie Adulte)

**POL S.**

Management of hepatitis c viral infection in hiv-positive patients taking antiretroviral treatment.  
*Presse Medicale*, 30 (14), 677-682, 2001  
(Services cités : Hépatologie Adulte)

Context: The prevalence of hepatitis C virus (HCV) infection in patients infected by the human immunodeficiency virus (HIV) varies from 10 to 30%, depending on the mode of contamination, and reaches about 80% in intravenous drug users and hemophiliacs. The two viral infections can be treated simultaneously or, on the contrary, one may be given priority depending on the respective pathological or viral situations. I Management of coinfections: HCV infection does not appear to affect the natural course of HIV infection. Inversely, HIV infection aggravates HCV infection by amplifying HCV replication. This leads to a risk of more severe liver disease and a more rapid progression to cirrhosis. Mortality in HIV-infected patients is higher. This points to the importance of early diagnosis and treatment aimed at avoiding progression to potentially severe liver disease. The impact of highly effective anti-HIV tritherapy regimens, particularly restoration of immune competence, and of drug-induced hepatitis on the natural history of HCV infection should be taken into consideration when making management decisions concerning implementation of antiretroviral or anti-hepatitis C treatments. Perspectives: The long-term efficacy of alpha-interferon given in a single-drug regimen has been mediocre. New perspectives have appeared with the development of new treatments, particularly the ribavirin-alpha-interferon combination or the development of delayed-release alpha-interferon. [References: 45]

**SOUSSAN P., POL S., GARREAU F., BRECHOT C., KREMSDORF D.**

Vaccination of chronic hepatitis b virus carriers with pres2/s envelope protein is not associated with the emergence of envelope escape mutants.

*J. Gen. Virol.*, 82 (Part 2), 367-371, 2001  
(Services cités : Hépatologie Adulte, U370)

PreS2/S vaccination of chronic hepatitis B virus (HBV) carriers led to a reduction in HBV replication or clearance of virus in 30% of treated patients. This study assessed whether vaccinothrapy of chronic HBV carriers induced the selection of escape mutants in the envelope 'a' determinant and whether envelope genetic variability might affect the response to vaccination. No amino acid differences were observed in the 'a' determinant between sequences obtained before and after treatment (five responders and seven nonresponders). However, alignment with HBV prototype sequences revealed seven amino acid changes. Two mutations (T140S and P127L) diverged from subtype variations. In the complete envelope sequence (five non-responders and five responders), ten amino acid modifications were detected between sequences obtained before and after treatment. The absence of any common mutations did not enable the definition of a hot spot of mutations implicated in the response to vaccination. Moreover, vaccinothrapy does not induce the selection of escape mutants in the 'a' determinant. [References: 25]

**2000**

**BRECHOT C.**

Hepatocellular carcinoma - introduction.

*Semin. Cancer Biol.*, 10 (3), 159, 2000  
(Services cités : U370, Hépatologie Adulte)

**BRECHOT C., GOZUACIK D., MURAKAMI Y., PATERLINI BRECHOT P.**

Molecular bases for the development of hepatitis b virus (hbv)-related hepatocellular carcinoma (hcc).

*Semin. Cancer Biol.*, 10 (3), 211-231, 2000  
(Services cités : U370, Hépatologie Adulte)

hepatocellular carcinoma (HCC) is the most common histological form of primary liver cancer, the tumor cells having retained features of hepatocytic differentiation. It is important to emphasize the heterogeneity of the histological background on which the tumor develops. Most HCCs complicate the evolution of an active or inactive cirrhosis.(1-4) However, some tumors occur on livers with minimal histological changes,(5) the prevalence of such cases varies from one geographical region to the other, being much higher in the southern half of Africa (around 40% of HCCs) than in Asia, America and Europe, where at least 90% of HCCs are associated in the cirrhosis. This heterogeneity is probably a reflection of different environmental and molecular studies have indeed clearly demonstrated the prime importance of environmental factors to the development of primary liver cancers in humans. Chronic hepatitis B (HBV) and C (HCV) infections are major risk factors. This review will mainly analyse the impact of chronic HBV infection but it is important to emphasize the potential synergistic effects between HBV and HCV, as well as between viral infections and other environmental factors, such as alcohol, chemical carcinogens (see review by Dr Wogan) and other, still poorly defined, hormonal factors which may account for the higher incidence of the tumor in man. Finally the review by Dr Buendia highlights the emerging issue of liver-cancer genetics. (C) 2000 Academic Press. [References: 230]

**CHRISTA L., PAULOIN A., SIMON M.T., STINNAKRE M.G., FONTAINE M.L., DELPAL S., OLLIVIER-BOUSQUET M., BRECHOT C., DEVINOY E.**

High expression of the human hepatocarcinoma-intestine-pancreas/pancreatic-associated protein (HIP/PAP) gene in the mammary gland of lactating transgenic mice. Secretion into the milk and purification of the HIP/PAP lectin.

*Eur. J. Biochem.*, 267 (6), 1665-1671, 2000  
(Services cités : U370, Hépatologie Adulte)

The human hepatocarcinoma-intestine-pancreas/pancreatic-associated protein (HIP/PAP) gene was previously identified because of its increased expression in primary liver cancers and during the acute phase of pancreatitis. In normal tissues, HIP/PAP is expressed both in endocrine and exocrine cells of the intestine and pancreas. HIP/PAP is a lactose binding C-type lectin which acts as an adhesion molecule for rat hepatocytes. The aim of the work was to study the HIP/PAP secretory pathway and to produce high levels of HIP/PAP in the milk of lactating transgenic mice. In view of its lactose C-type lectin properties, we have studied the consequences of the expression of HIP/PAP on mammary epithelial cells. In homozygous mice, production reached 11.2 mg.mL<sup>-1</sup> of milk. High levels of soluble and pure HIP/PAP (18.6 mg) were purified from 29 mL of milk. The purified protein was sequenced and the N-terminal amino acid of the mature HIP/PAP was identified as Glu27, thus localizing the site of cleavage of the signal peptide. The HIP/PAP transgene was only expressed in the mammary gland of lactating transgenic mice. HIP/PAP was detected by immunofluorescence in the whole gland, but labelling was heterogeneous between alveolar clusters, with strongly positive sparse cells. Using immuno

electron microscopy, HIP/PAP was observed in all the compartments of the secretory pathway within the mammary epithelial cells. We provide evidence that HIP/PAP is secreted through the Golgi pathway. However, the number of distended Golgi saccules was increased when compared to that found in wild-type mouse mammary cells. These modifications could be related to HIP/PAP C-type lectin specific properties.

**FONTAINE H., CHAIX M.L., LAGNEAU J.L., BRECHOT C., POL S.**

Recovery from chronic hepatitis c in long-term responders to ribavirin plus interferon alfa. *Lancet*, 356 (9223), 41, 2000

(Services cités : U370, Hépatologie Adulte)

In 45 sustained responders to interferon alfa and ribavirin, we found long-lasting elimination of hepatitis C virus RNA from serum and liver, together with histopathological improvement, suggesting complete recovery from chronic hepatitis C. [References: 5]

**FONTAINE H., THIERS V., CHRETIEN Y., ZYLBERBERG H., POUPON R.E., BRECHOT C., LEGENDRE C., KREIS H., POL S.**

Hbv genotypic resistance to lamivudine in kidney recipients and hemodialyzed patients. *Transplantation*, 69 (10), 2090-2094, 2000

(Services cités : U370, Transplantation & Réanimation Adulte, Hépatologie Adulte)

Background Lamivudine is a potent inhibitor of human immunodeficiency virus reverse transcriptase and hepatitis B virus (HEV) DNA polymerase. Its overall efficiency is clearly hampered by relapse at discontinuation and by risk of genotypic resistance. We describe herein the first cases of HBV resistance to lamivudine in kidney recipients and hemodialyzed patients. Methods. We analyzed 26 HBV-infected kidney recipients and five hemodialyzed patients treated with lamivudine who became serum HBV DNA-negative (by Digene test). The biological and virological follow-up identified breakthrough as defined by the reappearance of serum HBV DNA. In two cases of breakthrough, HBV DNA was amplified and sequenced through the polymerase domain, including the YMDD motif, before the beginning of treatment and at time of breakthrough to determine genotypic mutations. Results. Ten breakthroughs (reappearance of serum HBV DNA) were observed after a median follow-up of 11 months in eight kidney recipients and two hemodialyzed patients after a median duration of treatment of 16.5 (from 4 to 31) months of treatment. Previous HBe/anti-HBe seroconversion was not observed in the patients who escaped. In two kidney recipients, the comparison of HBV-DNA sequences before the treatment and after the breakthrough identified in one case a mutation of the highly conserved YMDD motif (YVDD), whereas in the second case, no genotypic mutation was observed in the sequenced region. Conclusion. We report the first cases of HBV genotypic resistance to lamivudine in kidney recipients and hemodialysis patients. Genotypic resistance is observed after 4-31 months of therapy. The YMDD mutation does not account for all cases of virological escape. [References: 29]

**KIRK G.D., CAMUS-RANDON A.M., MENDY M., GOEDERT J.J., MERLE P., TREPO C., BRECHOT C., HAINAUT P., MONTESANO R.**

Ser-249 p53 mutations in plasma DNA of patients with hepatocellular carcinoma from The Gambia.

*J. Nat. Cancer Inst.*, 92 (2), 148-153, 2000

(Services cités : Hépatologie Adulte)

BACKGROUND: A selective mutation, an arginine-to-serine substitution in codon 249, of the

p53 gene has been identified as a "hotspot" mutation in hepatocellular carcinoma (HCC). This mutation occurs in populations that are exposed to aflatoxins and have a high prevalence of hepatitis B virus carriers. We evaluated whether this mutation could be detected in cell-free DNA isolated from the plasma of subjects from The Gambia to detect this mutation that is strongly associated with HCC. **METHODS:** Fifty-three patients with HCC, 13 patients with cirrhosis, and 53 control subjects were prospectively recruited from The Gambia. Sixty patients, of non-African origin, with various liver pathologies were also selected from France. DNA was extracted and purified from 200-microL aliquots of plasma. The Ser-249 p53 mutation was detected by restriction endonuclease digestion of polymerase chain reaction products from exon 7 and was confirmed by direct sequencing of the amplified DNA. **RESULTS:** The Ser-249 p53 mutation was detected in plasma DNA from 19 (36%) of the 53 patients with HCC, two (15%) of the 13 patients with cirrhosis, and three (6%) of the 53 control subjects. This mutation was not detected in any plasma DNA from the European patients. The adjusted odds ratio for having the mutation was 16.4 (95% confidence interval = 3.0-90.5) for patients with HCC compared with the control subjects. **CONCLUSION:** The Ser-249 p53 mutation in plasma DNA is strongly associated with HCC in Gambian patients. This mutation was also detected at a much lower prevalence in plasma DNA from Gambian patients with cirrhosis and in Gambian control subjects, findings that may lead to the earlier detection of HCC. Use of the Ser-249 p53 mutation should facilitate further molecular epidemiologic studies on the development of HCC.

**NALPAS B., ZYLBERBERG H., DUBOIS F., PRESLES M.A., GILLANT J.C., LIENARD M., DELEMOTTE B., BRECHOT C.**

Prevalence of infection by hepatitis viruses in a rural area. analysis according to risk factors and alcohol consumption.

*Gastroentérol. Clin. Biol.*, 24 (5), 536-540, 2000

(Services cités : U370, Hépatologie Adulte)

**Objectives** - To evaluate the prevalence of serum markers of hepatitis A, B and C viruses in a rural area according to risk factors and alcohol consumption. **Methods** - Transversal study of unselected subjects living and working in a rural area. Each subject included was asked to fill out an anonymous self-administered questionnaire dealing with his own risk factors, sexual behaviour and alcohol consumption. A blood sample was collected for detection of HBsAg, anti-HBc, anti-HBs, anti-HAV and anti-HCV antibodies. **Results** - Three hundred three subjects with a mean age of 48 years were included. Main risk factors for viral infection were: transfusion (9.4%), intravenous drug addiction (0.73%), acupuncture (17.5%), tattoos (5.8%), past hospitalizations (71.5%), homosexuality (1.1%), conjugal unfaithfulness (11%), sexual partners >5 (21.3%). Most subjects with at risk sexual behaviour had sexual relations without protection. Anti-HAV prevalence was 87.2% (95% confidence interval 83.4-91.0%). None of the subjects was HBsAg positive and 6.0% (confidence interval 4.7-8.7%) had anti-HBV antibodies. HBV prevalence was correlated to homosexuality only. Two subjects (0.67%, confidence interval 0-1.6%) without any identified risk factor had anti-HCV antibodies. There was no correlation between serum viral marker positivity and an excess alcohol consumption (>80g of ethanol/d) which was present in 46 subjects. However HBV prevalence was 28.6% in the seven subjects who had been treated for alcoholism; these 7 subjects had a highly at risk sexual behaviour. **Conclusion** - In a rural area, infection by HAV is very frequent. The prevalence of HBV and HCV did not greatly differ from that observed in the general and urban population. The frequent failure to use protection in subjects with at risk sexual behaviour reinforces the need of prevention programs in rural areas. [References: 17]

**NEVEUX N., de BANDT J.P., FATTAL E., HANNOUN L., POUPON R., CHAUMEIL J.C., DELATTRE J., CYNOBER L.A.**

Cold preservation injury in rat liver: effect of liposomally-entrapped adenosine triphosphate.  
*J. Hepatol.*, 33 (1), 68-75, 2000

(Services cités : Hépatologie Adulte)

Background/Aims: Energy charge and capacity for adenosine triphosphate (ATP) synthesis have been demonstrated to play a major role in the maintenance of organ function after liver preservation for transplantation. The aim of this study was to evaluate whether a supply of liposomally-entrapped ATP during preservation could improve the energy state and metabolism of cold-stored rat liver. Methods: In the first set of experiments, the uptake of ATP-containing liposomes and their effects on hepatic viability were determined in isolated perfused unstored rat liver, In the second set of experiments, rat livers were preserved for 18 h at 4 degrees C in UW solution in the presence of these liposomes, and effects on energy state, cell volume and metabolism were evaluated, In each part, data were compared with adequate control, unloaded liposome-treated, and free ATP-treated groups (n=6 in each group), Results: In non-stored livers, ATP-containing liposomes were taken up by the liver; they did not alter hepatic viability and induced a decrease in energy substrate consumption (glucose and amino acids), and an improvement in intrahepatic ATP content (+23% vs, Control), Addition of liposomally-entrapped ATP during cold storage produced a significant attenuation of the decrease in hepatic ATP content (Lip ATP 2: 524+/-45 vs, Control 2: 364+/-106 nmol/g; p<0.05), and induced, during reperfusion, a decrease in proteolysis associated with an increase in cell volume compared with the other groups (Lip ATP 2: 633+/-63 vs. Control 2: 532+/-38, Unloaded Lip 2: 483+/-55 and Free ATP 2: 500+/-29 mu l/g; p<0.01). Conclusions: These data indicate that liposomally-entrapped ATP represents an effective means to improve liver graft energy state and function, The decrease in protein degradation may be related to the modification of cell volume.  
[References: 42]

**PERLEMUTER G., SABILE A., BRECHOT C.**

Interactions between hepatitis c virus and lipid liver metabolism.  
*Gastroentérol. Clin. Biol.*, 24 (5), 547-553, 2000

(Services cités : U370, Hépatologie Adulte)

**POL S.**

in: *Les Hépatites Virales*. (Pol S. eds.)

Doin (Paris), 2000, pp..

(Services cités : Hépatologie Adulte, U370)

**POL S., MICHEL M.L., BRECHOT C.**

Immune therapy of hepatitis b virus (hbv) chronic infection. european experience.

*Acta Gastro-Enterol. Belg.*, 63 (2), 194-196, 2000

(Services cités : U370, Hépatologie Adulte)

**POL S., ZYLBERBERG H.**

Treatment of viral hepatitis in drug users.

*Ann. Méd. Intern.*, 151 (Suppl A), A33-A39, 2000

(Services cités : Hépatologie Adulte)

Management of viral hepatitis in drug users must follow a multidisciplinary approach within the framework of overall psychosocial, alcoholic, and medical care. Substitution is an important but not indispensable aspect. In patients who have achieved social, psychological and medical stability (possible initiation of antiretroviral treatment), antiviral treatments can be started and followed in the same way as for other patients. Prescriptions should aim at improving the liver disease and avoid progression to cirrhosis and complications. Ribavirin/interferon-alfa appears to be the combination of choice for first line treatment of hepatitis C (while waiting for combinations with protease inhibitors). Anti-HBV vaccination is the treatment of choice for the prevention of hepatitis B and D, Coordination and information sharing between health and social care partners is crucial for the management of these patients. [References: 39]

**POL S., NALPAS B., BOURLIERE M., COUZIGOU P., TRAN A., ABERGEL A., ZARSKI J.P., BERTHELOT P., BRECHOT C.**

Combination of ribavirin and interferon-alfa surpasses high doses of interferon-alfa alone in patients with genotype-1b-related chronic hepatitis c.

*Hepatology*, 31 (6), 1338-1344, 2000

(Services cités : U370, Hépatologie Adulte)

The purpose of this study was to compare interferon-alfa alone (12-month course with high initial doses) with a combination of interferon-alfa and ribavirin in patients infected with genotype 1b. Three hundred and seven patients were randomized into 3 groups to receive 6 mega units (MU) of interferon-alfa-2b subcutaneously 3 times weekly for 6 months followed by 3 MU for 6 months (n = 95, group A); 10 MU for 3 months followed by 6 MU for 3 months, followed by 3 MU for 6 months (n = 83, group B); or the: group-A schedule in combination with ribavirin (n 129, group C) for 4 (n = 46), 6 (n = 44), or 12 months (n = 39). Negative polymerase chain reaction (PCR) was more frequent in group C than in groups A or B after 3 months of treatment (P <.006), at the end of treatment (P =.017), and at the end of follow-up (32.8%, 16.9%, and 14.1%, respectively, P <.003). A complete response (negative PCR and normal alanine transaminase) was higher in group C than in the other groups and when comparing 12- to 4- and 6-month combination therapy at the end of treatment (P =.05) and of follow-up (45.2% vs. 25.4%, respectively, P =.05). The greater efficacy of the combination was related to the higher rate of primary virological response and also to a decrease in the percentage of breakthrough and of relapse. In 1b-infected patients, the combination of high doses of interferon-alfa (6 MU) and ribavirin for 12 months appears to be the best therapy, with a high rate of sustained response. [References: 26]

**POL S.**

Treatment of hepatitis c virus infection in dialysis patients.

*Nephrol. Dialysis Transplant.*, 15 (Suppl 8), 46-48, 2000

(Services cités : Hépatologie Adulte)

**POL S., ZYLBERBERG H.**

Clinical forms and prognosis of hepatitis C.

*Rev. Prat.*, 50 (10), 1083-1088, 2000

(Services cités : Hépatologie Adulte)

Hepatitis C virus infects around 600,000 French people, mainly after parenteral exposure (in association with transfusion before 1990 and with intravenous drug use). Spontaneous resolution at the acute stage of the infection occurs in around 30% of cases while chronic infection is

observed in around 70% of cases and its main risk is evolution to cirrhosis. Three predictive factors of cirrhosis have been identified: the duration of infection (greater than 20 years), the age at contamination (greater than 40 years) and a chronic alcohol consumption (> 80 g/day). Immunosuppressive situations (drug-related immune suppression for the prevention of graft rejection in allograft recipients or human immune deficiency virus-coinfection) as well as hepatitis B virus coinfection enhance the risk of cirrhosis and reduce the time of occurrence of cirrhosis. These predictors have to be considered in the information to the patients and in therapeutic decisions. They explain that any hepatitis C virus-infected patient has to undergo a liver biopsy to evaluate the necro-inflammatory activity and the fibrosis of the liver disease to delineate the place of a follow-up with a control of aggravation factors (alcohol discontinuation) and of an antiviral therapy.

**POL S., SAMUEL D., CADRANEL J.F., LEGENDRE C., BISMUTH H., BRECHOT C., KREIS H.**

Hepatitis and solid organ transplantation.

*Transplant. Proc.*, 32 (2), 454-457, 2000

(Services cités : Hépatologie Adulte, U370)

**TUVERI R., PERRET J.L., DELAPORTE E., NGUEMBY-MBINA C., D'ALLONES L.R., HENZEL D., FAIVRE D., SCARPA B., CONTU P., COLOMBO M., THIERS V., BRECHOT C., LAROUZE B.**

Prevalence and genetic variants of hepatitis gb-c/hg and tt viruses in gabon, equatorial africa.

*Amer. J. Trop. Med. Hyg.*, 63 (3-4), 192-198, 2000

(Services cités : Hépatologie Adulte, U370)

The distribution of Hepatitis GB-C/HG (GB-C/HG) and TT viruses (TTV) infections was investigated in selected populations from Gabon using Polymerase Chain Reaction (PCR) and Enzyme Linked Immunosorbent Assay (ELISA) for anti-Envelop 2 (anti-E2) GBV-C/HGV antibodies. Among pregnant women, 29 of 229 (12.6%) were Hepatitis GB virus-C and Hepatitis G virus (GBV-C/HGV) RNA positive (+) and 32 of 81 (39.5%) anti-E2 + versus 8 of 39 (20.5%) TTV DNA +. Among sickle cell anemia patients, 9.7% (3/31) were GBV-C/HGV RNA + versus 22.5% (7/31) TTV DNA +. For tuberculosis patients, the figures were 11.5% (4/35) and 0%. A study of hepatocellular carcinoma cases (n = 27) versus controls (n = 66) did not show significant differences Tol GBV-C/HGV RNA (10.7% versus 12.1%) and TTV DNA (44.4% versus 30.3%). According to phylogenetic analysis, the 15 GBV-C/HGV strains investigated clustered in group 1, the most common in sub-Saharan Africa whereas TTV sequences (n = 4) mostly clustered in genotypes G1 and one close to genotype G3. In the Gabonese populations investigated, GBV-C/HGV and TTV infections were highly endemic. These data are consistent with the low pathogenicity of these agents. [References: 50]

**ZYLBERBERG H., NALPAS B., POL S., BRECHOT C., VIARD J.P.**

Is there a relationship between hepatitis c virus infection and antiretroviral-associated lipotrophy ?

*AIDS*, 14 (13), 2055, 2000

(Services cités : Hépatologie Adulte, Immunologie Clinique Adulte)

**ZYLBERBERG H., CHAIX M.L., BRECHOT C.**

Infection with hepatitis c virus genotype 4 is associated with a poor response to interferon-alpha.

*Ann. Intern. Med.*, 132 (10), 845-846, 2000  
(Services cités : Hépatologie Adulte)

**ZYLBERBERG H., FONTAINE H., CORREAS J.M., CARNOT F., BRECHOT C., POL S.**  
Dilated bile duct in patients receiving narcotic substitution - an early report.

*J. Clin. Gastroenterol.*, 31 (2), 159-161, 2000

(Services cités : Radiologie Adulte, Hépatologie Adulte, U370)

Narcotic substitution is now widely used. Morphine can induce a spasm of the sphincter of Oddi but dilation of bile duct has been reported only in an anecdotal case. In June 1995, we observed a first case of dilation of the common bile duct without organic obstacle in a hepatitis C virus (HCV)-infected patient who was under narcotic substitution, suggesting a causal relationship. We conducted a prospective study to evaluate the precise prevalence of bile duct abnormalities related to narcotic substitution in active intravenous drug or ex-intravenous drug users referred to our liver unit for histologic evaluation of HCV infection. We conducted a prospective study in a 30-month period of 334 HCV-infected patients, including 36 receiving narcotic substitution with methadone or buprenorphine. Biliary tract was analyzed by ultrasonography and by endoscopy ultrasound in cases of bile duct abnormalities. Of the 36 patients under narcotic substitution, 3 (8.3%) had asymptomatic dilated bile duct without organic obstacle-defined as a common bile duct greater than or equal to 9 mm-compared to 1 of 298 (0.03%;  $p < 0.001$ ) of those who did not receive substitution. Narcotic substitution may lead to bile duct dilation that does not require invasive diagnosis procedures. [References: 8]

**1999**

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Lack of association between HCV infection and HIV-related lymphoma.

*Br. J. Haematol.*, 105 (2), 568-569, 1999

(Services cités : Hépatologie Adulte, Hématologie Adulte)

**CHRISTA L., SIMON M.T., BREZAULT-BONNET C., BONTE E., CARNOT F., ZYLBERBERG H., FRANCO D., CAPRON F., ROSKAMS T., BRECHOT C.**

Hepatocarcinoma-intestine-pancreas/pancreatic associated protein (HIP/PAP) is expressed and secreted by proliferating ductules as well as by hepatocarcinoma and cholangiocarcinoma cells.

*Amer. J. Pathol.*, 155 (5), 1525-1533, 1999

(Services cités : U370, Hépatologie Adulte)

Hepatocarcinoma-intestine-pancreas/pancreatic associated protein (HIP/PAP) gene was identified because of its increased expression in 25% of human hepatocellular carcinoma. HIP/PAP protein, a C-type lectin, binds laminin, acts as an adhesion molecule for hepatocytes, and has also been described as an acute phase secretory protein during acute pancreatitis in humans and rats. We investigated HIP/PAP protein expression in patients with various liver diseases associated with ductular reaction. At the same time, we analyzed patients with hepatocellular carcinoma and cholangiocarcinoma, and tested HIP/PAP protein levels in sera to establish the pattern of secretion. Our data show that HIP/PAP expression was not restricted to hepatocellular carcinoma, but was also detected in cholangiocarcinoma cells as well as in reactive non-malignant bile ductules. In contrast, HIP/PAP protein expression was undetectable in normal mature hepatocytes, but some ductular cells localized at the interface of portal tracts with parenchyma were HIP/PAP immunoreactive in normal liver. Finally, we present evidence that HIP/PAP

serum levels were increased in 21/28 (75%) patients with hepatocellular carcinoma, and in 25/51 (49%) patients with nonmalignant cirrhosis. Altogether, these results suggest that HIP/PAP protein may be implicated in hepatocytic and cholangiolar differentiation and proliferation.

**FONTAINE H., THIERS V., POL S.**

Hepatitis B virus genotypic resistance to lamivudine.

*Ann. Intern. Med.*, 131 (9), 716-717, 1999

(Services cités : Hépatologie Adulte)

**FONTAINE H., POL S.**

The Hepatitis Interventional Therapy Group. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C.

*Gastroentérol. Clin. Biol.*, 23 (4), 541-544, 1999

(Services cités : Hépatologie Adulte)

**MOMMEJA-MARIN H., ZYLBERBERG H., POL S.**

Prophylactic hepatitis B vaccination: present and future.

*Gastroentérol. Clin. Biol.*, 23 (4), 452-463, 1999

(Services cités : U370, Hépatologie Adulte)

**POL S., COUZIGOU P., BOURLIERE M., ABERGEL A., COMBIS J.M., LARREY D., TRAN A., MOUSSALLI J., POUPON R., BERTHELOT P., BRECHOT C.**

A randomized trial of ribavirin and interferon-alpha vs. interferon-alpha alone in patients with chronic hepatitis C who were non-responders to a previous treatment.

*J. Hepatol.*, 31 (1), 1-7, 1999

(Services cités : Hépatologie Adulte)

Background/Aim: Fifty percent of patients infected with hepatitis C virus (HCV) show no response to alpha-interferon, and no alternative therapy has thus far proven to be effective.

Therapeutic combination with ribavirin and alpha-interferon has shown promising results in naive patients and in relapsers, but based on limited series, it was reported to be inefficient in non-responders. The aim of our study was therefore to explore and compare, in a randomized trial, the tolerance and potential efficacy of alpha-interferon alone with a sequential combination of ribavirin and the same alpha-interferon regimen in those patients.

**POL S.**

What are the risks involved in kidney transplantation that is probably hepatitis B related.

*Pediat. Nephrol.*, 13 (8), 720, 1999

(Services cités : Hépatologie Adulte)

**POL S., ZYLBERBERG H., FONTAINE H., BRECHOT C.**

Treatment of chronic hepatitis c in special groups.

*J. Hepatol.*, 31 (Suppl 1), 205-209, 1999

(Services cités : U370, Hépatologie Adulte)

Little is known about treatment of hepatitis C virus (HCV) infection in "other groups" than the general population, namely patients with hematologic or renal disorders and patients with human immune deficiency (HIV) co-infection, The aim was to better define HCV therapies in these groups, We analyzed the medical literature focusing on treatment of HCV infection in other

populations to suggest conclusions about indications based on tolerance and efficacy, As in the general population, the decision to treat should be based mainly on liver pathology, and to a lesser extent on virologic profiles (genotype, quantitative viremia), Hemophilia does not modify therapeutic strategies which combine interferon-alpha and ribavirin. Similar combinations should be discussed in patients with inherited hemoglobin disorders but iron overload (secondary hemochromatosis) associated with multiple transfusions may decrease the potential efficacy of interferon-alpha and chronic anemia may limit the use of ribavirin, In hemodialyzed patients, therapy by interferon-alpha is feasible with 3 MU subcutaneously after each hemodialysis three times weekly for 6-12 months. Virologic results are at least similar to those obtained in the general population with frequent pathological improvement, Combinations are not possible because ribavirin is contraindicated for pharmacokinetic reasons, In kidney recipients, interferon-alpha is deleterious and inefficient; ribavirin monotherapy has a potential interest which remains to be evaluated, In HIV co-infected patients, treatment is mandatory given the high rate of cirrhosis and the improved survival related to multiple anti-HIV therapies (which have no clear efficacy for quantitative HCV viremia), Due to the limited efficacy of interferon-alpha monotherapy, the combination of interferon-alpha and ribavirin appears to be the logical treatment, An important point is the in vitro inhibition of phosphorylation by ribavirin of HIV reverse transcriptase inhibitors which has to be analyzed in vivo before the combination can be recommended. On the basis of the results of liver biopsy, antiviral treatments may be proposed for HCV-infected patients with hematologic or renal disorders as well as for HIV co-infected patients, The choice of therapy (monotherapy or combined therapies) should be based on the clinical situation (contraindicated with chronic anemia or renal failure, for example) and its duration on the virologic factors of response as in the general population. [References: 35]

**ROSMORDUC O., PATERLINI P., POUPON R., BRECHOT C.**

Hepatitis viruses and hepatocellular carcinoma.

*Gastroentérol. Clin. Biol.*, 23 (3), 363-375, 1999

(Services cités : U370, Hépatologie Adulte)

**ZYLBERBERG H., POL S.**

Coinfection of hepatitis C virus and human immunodeficiency virus and antiretroviral multitherapies.

*Gastroentérol. Clin. Biol.*, 23 (8-9), 878-881, 1999

(Services cités : Hépatologie Adulte)

**ZYLBERBERG H., THIERS V., LAGORCE D., SQUADRITO G., LEONE F., BERTHELOT P., BRECHOT C., POL S.**

Epidemiological and virological analysis of couples infected with hepatitis C virus.

*Gut*, 45 (1), 112-116, 1999

(Services cités : Hépatologie Adulte)

**BACKGROUND:** If transmission of hepatitis C virus (HCV) infection through parenteral exposure is well documented, sexual transmission of HCV is still debated. **AIMS:** To perform extensive epidemiological and virological analysis in 24 couples in which each spouse was anti-HCV positive in order to delineate more precisely potential sexual transmission of HCV.

**PATIENTS:** Twenty four couples in which each partner was anti-HCV positive. These 48 spouses were recruited in a liver unit by regular screening of spouses of index patients.

**METHODS:** All 48 spouses completed an epidemiological questionnaire on risk factors for HCV.

Qualitative detection of serum HCV RNA and determination of HCV type by genotyping and serotyping were performed. Sequence analysis of HCV strains by phylogenetic analysis was carried out in seven couples with concordant genotypes. RESULTS: The mean (SD) partnership duration was 12 (10) years. Serum HCV RNA was detected in both partners in 18 of the couples (75%) and in only one partner in six of the couples (25%). HCV typing showed concordant genotypes in 12 couples (50%), discordant genotypes in seven (29%), and in the other five couples (21%) only one spouse could be genotyped. Of the 48 spouses, 33 had a major risk factor for HCV transmission such as transfusion (n = 6) and intravenous drug use (n = 27). Eleven of the 12 couples infected with the same HCV genotype had at least one parenteral risk factor for viral transmission in both spouses. Whatever the genotype concordance, in most couples (75%), both spouses showed parenteral risk factors for viral transmission. Sequence analysis of HCV strains was possible in seven of 12 couples with identical genotype and showed different and identical isolates in four and three couples respectively. CONCLUSION: The study emphasises the risk of overestimating the importance of a very low sexual HCV transmission risk as against other, mainly parenteral, risk factors.

**ZYLBERBERG H., POL S., THIERS V., CHAIX M.L., LAGORCE D., BRECHOT C., NALPAS B., BERTHELOT P.**

Significance of repeatedly normal aminotransferase activities in HCV-infected patients.

*J. Clin. Gastroenterol.*, 29 (1), 71-75, 1999

(Services cités : Hépatologie Adulte)

The significance of repeatedly normal serum aminotransferase activities in antihepatitis C virus (anti-HCV)-positive patients is not clear. To address this issue, the authors analyzed clinical, virologic, histopathologic, and biological characteristics of such subjects. Among their active file of 1,200 anti-HCV-positive immunocompetent patients, they identified 36 subjects (3%) with repeatedly normal aminotransferase activities, as defined by at least four normal values of aminotransferase over a minimum period of 6 months without any abnormal value (mean of this period, 31 +/- 21 months). The 36 patients included 11 men and 25 women with a mean age of 45 +/- 15 years. Twenty-three of these 36 subjects (64%) had detectable HCV viremia by polymerase chain reaction. Their genotype distribution was as follows: genotype 1a or 1b, 57%; genotype 2, 26%; and genotype 3, 17%. Of the HCV ribonucleic acid (RNA)-positive and HCV RNA-negative subjects, 17 and 5 had a liver biopsy respectively. In the former, the mean Knodell score was 5.6 +/- 3.5 (range, 1 to 14), and was <5 in 9 patients (53%) and greater than or equal to 5 in 8 (47%), including extensive fibrosis (n = 2) or cirrhosis (n = 2). In the HCV RNA-negative subjects, one patient had a Knodell score greater than or equal to 5. Comparing the 23 immunocompetent viremic subjects with repeatedly normal serum aminotransferase activities with our group (n = 564) of immunocompetent viremic patients with abnormal aminotransferase activities, there was a significant predominance of women (70% versus 44%, p < 0.05) and of genotype 2 in the former (26% versus 7%, p < 0.05), but no differences according to quantitative viremia, alcohol consumption, or distribution of risk factor were observed. Most of viremic HCV-infected patients with long-term and repeatedly normal aminotransferase values have indeed chronic active hepatitis, including extensive fibrosis or cirrhosis in as many as 20% of patients. This emphasizes the need for serum HCV RNA determination in anti-HCV-positive patients with normal aminotransferase activities. In these patients liver biopsy may be necessary and should be discussed. [References: 19]

**ZYLBERBERG H., RIMANIOL A.C., POL S., MASSON A., de GROOTE D.,**

**BERTHELOT P., BACH J.F., BRECHOT C., ZAVALA F.**

Soluble tumor necrosis factor receptors in chronic hepatitis C: a correlation with histological fibrosis and activity.

*J. Hepatol.*, 30 (2), 185-191, 1999

(Services cités : Hépatologie Adulte, U025)

Background/Aims: Tumor necrosis factor-alpha (TNF) is a mediator of inflammation and cellular immune response. Soluble TNF receptors (sTNFR) sTNF-R55 and sTNF-R75, which compete with cellular receptors for the binding of TNF, have been detected at high levels in infectious diseases including human immunodeficiency virus and HBV infection. In order to investigate the activation of the TNF system in HCV infection, we have analyzed the balance between TNF and sTNF-R in 60 HCV-infected subjects according to their clinical, biological, virological and histological characteristics.

**ZYLBERBERG H., FONTAINE H., THEPOT V., NALPAS B., BRECHOT C., POL S.**

Triggering of acute alcoholic hepatitis by alpha-interferon therapy.

*J. Hepatol.*, 30 (4), 722-725, 1999

(Services cités : Hépatologie Adulte)

Background/Aims: Alcohol may induce autoimmunity by recognition of acetaldehyde-modified proteins which may be implicated in the pathogenicity of acute alcoholic hepatitis. We report here the potential role of alpha-interferon, a potent inducer of the autoimmunity process, in inducing alcoholic hepatitis.