Parallel Session 14: HEPATOBILIARY TRANSPORT AND CHOLESTATIC LIVER DISEASES

123 PRESENTATION AND NATURAL HISTORY OF PRIMARY BILIARY CIRRHOSIS IN SPAIN: EXPERIENCE OVER 35 YEARS

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Background and Aims: The natural history of primary biliary cirrhosis (PBC) generally relies on data gathered years ago. Since the presentation and course of PBC may have changed in the last years, we have analysed a cohort of patients followed from the seventies to July 2006 in 16 hospitals from Spain.
Patients and Methods: 1094 patients (962 female; mean age: 53.1±0.4 years) diagnosed with PBC. The clinical features and histological stage at presentation, incident characteristics of disease progression, including jaundice, ascites, variceal bleeding and hepatic encephalopathy, and the outcome, including death or liver transplantation, were recorded. To determine differences over the years, the overall series was divided into 7 groups according to the date of diagnosis, which comprise periods of approximately 5 years.
Results: There were significant differences in the presentation of PBC among the periods. Thus, age at diagnosis increased progressively during the study period. Pruritus, melanoderma, jaundice, ascites, and encephalopathy were significantly less frequent in the patients from the last fifteen years than in patients diagnosed before 1990 ($p < 0.001$). The histological stage was less advanced in the last two decades, particularly in the last three 5-year periods ($p < 0.001$). Moreover, the incident features of disease progression were less frequent in the last periods. 122 patients (11.9%) died, and 64 (6.2%) liver transplanted. There were significant differences in the survival free of liver transplantation among the study periods, since the 10-year survival in the consecutive periods were 50%, 73%, 86%, 90% and 89% ($p < 0.001$). Most patients diagnosed in the last 20 years were treated with UDCA.
Conclusions: The current presentation of PBC is certainly less severe than it was years ago, as well is the incidence of features of disease progression. The survival free of liver transplantation is also better, probably influenced by lower severity at diagnosis and treatment with UDCA.

124 HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY COMPLETELY ABROGATES CHOLANGITIS IN THE NOD.C3C4 MOUSE MODEL OF PBC

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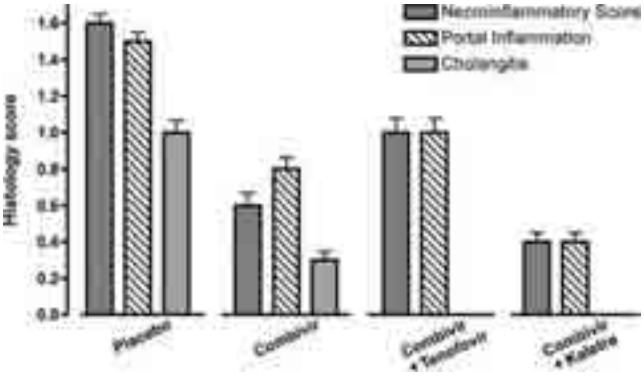
A recent randomized controlled trial using Combivir (zidovudine and lamivudine) showed that patients with PBC developed significant improvement in hepatic biochemistry and clinical scores with decreased detection of human betaretrovirus in serum. The related retrovirus, mouse mammary tumor virus (MMTV) has been found in bile ducts of the NOD.c3c4 mouse model of PBC.
Our aim was to investigate whether combination and highly active antiretroviral treatment (HAART) impacts on biliary disease in the NOD.c3c4 mouse.
Methods: weanling NOD.c3c4 mice were treated to 20 weeks of age with (i) placebo, (ii) Combivir, (iii) Combivir and tenofovir and (iv) Kaletra (lopinavir and ritonavir) and Combivir using 10 mice per treatment.
Results: Antiviral therapy improved necroinflammatory score, portal inflammation and cholangitis ($p < 0.0001$). Combinations (iii) and (iv) completely abrogated cholangitis but tenofovir showed no other benefit when added to Combivir. Hepatic viral levels were lowered 29% with (iii) Combivir and tenofovir ($p < 0.05$) and 40% with (iv) Combivir and Kaletra ($p < 0.01$) compared to placebo. Serial hepatic biochemistry studies showed significant improvements in alkaline phosphatase ($p < 0.05$) and AST ($p < 0.002$) with the greatest reduction in mice treated with (iv) Combivir and Kaletra.



Conclusions: The detection of MMTV in the NOD.c3c4 mouse and resolution of biliary disease with antiviral therapy supports the retroviral hypothesis for PBC. The HAART regimen using Kaletra with Combivir resulted in the lowest viral levels, hepatic biochemistry and histology scores with complete abrogation of cholangitis. The present studies suggest that HAART may be able to inhibit the human betaretrovirus sufficiently to justify a controlled trial in patients with PBC and human betaretrovirus infection.

125 SIDE CHAIN MODIFIED BILE ACIDS MODULATE ENDOPLASMIC RETICULUM STRESS IN MDR2$^{-/-}$ MICE IN VIVO AND BILE DUCT EPITHELIAL CELLS IN VITRO

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Background and Aims: Phospholipid biosynthesis occurs on the cytosolic site of the endoplasmic reticulum (ER). A liver specific phospholipid flippase Mdr2/Abcb4 facilitates the biliary excretion of PC. Interestingly, mice lacking Mdr2 neither accumulate PC in liver nor show elevated levels of PC in plasma. However, this mouse model is characterized by biliary fibrosis, chronic inflammation and oxidative stress surrounding the bile ducts. 4-Hydroxynonenal (4-HNE) a major product of lipid peroxidation was recently shown to mediate ER-stress. Moreover, proteomic analysis of Mdr2$^{-/-}$ mice has revealed an induction of Grp78/Bip, a chaperone protein contributing to ER stress (Henkel et al. 2006). Since we have recently demonstrated that the increased 4-HNE staining surrounding the bile ducts of Mdr2$^{-/-}$ mice was diminished by the treatment with 24-norursodeoxycholic acid (norUDCA), we aimed to test the hypothesis that treatment with norUDCA directly alleviates ER-stress in bile duct epithelial cells.
Methods: Microarray technology and Q-PCR were performed to screen for ER-stress-associated genes in wild type, Mdr2$^{-/-}$ and mice treated with norUDCA. Western blot analysis was used to investigate posttranscriptional effects of norUDCA on ER-stress, while direct effects on ER-stress