Hepatitis in The World

Outcomes of interferon α and Ribaverin treatment for chronic hepatitis C in patients with normal serum aminotransaminases

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Introduction: Information on treatment outcomes with Interferon plus Ribaverin combination therapy in chronic hepatitis C patients with normal alanine aminotransaminase (ALT) levels is limited. **Aim**: The aims of this study were to assess outcomes of treatment with interferon plus Ribaverin in patients with normal ALT levels (normal ALT group, n=52) compared with those with elevated ALT levels (raised ALT group, n=53), and to document the rate at which patients with normal ALT levels have an apparent worsening of disease, as shown by increases in ALT levels .**Results**: At the end of treatment (week 48), 31 patients (59.6%) in the normal ALT group and 30 patients (56.6%) in the raised ALT group had undetectable hepatitis C virus (HCV) RNA (p=0.75). A sustained virological response (SVR) was achieved in 20 patients (38.5%) in the normal ALT group and in 21 patients (39.6%) in the raised ALT group (p=0.90). Patients were subsequently followed up for a median of 29.8 (interquartile range 25th–75th percentile (IQR) 20.8–36.2) months in the normal ALT group and for a median of 26.1 (IQR 17.7–36.3) months in the raised group (p=0.20) after week 72 of treatment. Among patients without SVR in the normal ALT group, only three patients (9.4%) developed persistently raised ALT levels following therapy. **Conclusions**: Combination therapy with interferon plus Ribaverin is associated with a similar SVR in patients with normal ALT levels compared with those with elevated ALT levels. In patients with normal ALT levels, virological non-response to therapy results in new elevations in serum ALT levels in a small minority only.

Clinical outcome and virologic profiles of severe hepatitis B exacerbation due to YMDD mutations

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Background/Aims: To study the outcome and the virologic profiles of severe hepatitis exacerbations due to YMDD mutants in lamivudine-treated patients. **Methods**: Eighteen lamivudine-treated patients with severe hepatitis exacerbations due to YMDD mutants were recruited. Laboratory and clinical parameters were monitored. Viral genotypes and YMDD mutations were determined. **Results**: None of the 18 patients had YMDD wild-type during exacerbations. Three (17%) and 15 (83%) patients had genotypes B and C, respectively. Elevated bilirubin levels and prolonged prothrombin time were found in 11 (61%) and six patients (33%) respectively. Three patients (17%) had adverse outcome with the development of ascites and/or encephalopathy. One of these patients required liver transplantation and one died. Both patients had evidence of cirrhosis before treatment and hepatitis B e antigen (HBeAg) seroreversion from anti-HBe positivity. The remaining 16 patients (89%) have no evidence of pre-existing cirrhosis. Thirty seven percent of patients had normal alanine aminotransferase levels at the last follow-up. The median HBV DNA level at the last follow-up was significantly lower than the pre-treatment level (P=0.009). **Conclusions**: Though the majority of patients with severe hepatitis exacerbations due to YMDD mutants had uneventful course, early liver transplantation should be considered in patients with pre-existing cirrhosis and HBeAg seroreversion.

Hepatitis B DNA vaccine induces protective antibody responses in human non-responders to conventional vaccination

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A novel DNA vaccine against hepatitis B virus was administered intraepidermally by particle-mediated epidermal delivery (PMED) to 16 human subjects who demonstrated absent or non-sustainable responses to conventional hepatitis B vaccination. Eleven subjects received three doses of vaccine at 56-day intervals, and five subjects received only a single vaccination. Each dose of vaccine contained 4 μg of plasmid DNA encoding the hepatitis B surface antigen (HBsAg). The vaccine was safe and well tolerated. Remarkably, the DNA vaccine elicited antibody responses in 12 of the 16 subjects after a licensed subunit vaccine failed to induce a lasting response after ≥3 vaccinations. This study provides evidence in humans for protective immunogenicity of a particle-mediated DNA vaccine in subjects who have responded suboptimally to conventional vaccination.

HBcAg-specific cytokine production by CD4 T lymphocytes of children with acute and chronic hepatitis B

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In the presented studies HBcAg-specific cytokine production (IFN-γ, IL-2, IL-4, IL-5 and IL-10) was evaluated, by Th lymphocytes isolated from peripheral blood of children with acute or chronic B hepatitis. Moreover, effect of IL-10 neutralization was examined on HBcAg-induced secretory response of Th lymphocytes obtained from children with chronic B hepatitis. The studies were performed on 12 children with acute self-limited B hepatitis and 20 children with chronic active B hepatitis. CD4 T cells were isolated from peripheral blood of the patients, cultured for 48 h in presence of rHBcAg or in its absence (control). Production of studied cytokines was monitored using ELISPOT and ELISE assays. The course of acute self-limited B hepatitis was associated with preferential Th1-type response, manifested by elevated production of IFN-γ and IL-2. On the other hand, in chronic B hepatitis a diminished response to HBcAg of both Th1 and Th2 types was disclosed, characterized by very low secretion of IFN-γ, IL-2, IL-4 and IL-5. In parallel, preferential antigen-specific production of IL-10 was noted and its suppressive effect on HBcAg-induced response of Th1 cells. The results permitted to conclude that in children with acute self-limited B hepatitis preferential HBcAg-specific activation of Th1 lymphocytes may be of significance for efficient anti-HBV immune response. On the other hand, development of chronic B infection in children seems to be determined by disturbed HBcAg-specific functions of both Th1 and Th2 cells whereas activity of the disease may be controlled by anti-inflammatory response of antigen-presenting cells and/or of regulatory CD4 T lymphocytes, involving IL-10 production.

A randomized trial of consensus interferon in combination with Ribaverin as initial treatment for chronic hepatitis C

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Background/Aims: The aim of the present, open-labeled, randomized study was to determine the efficacy and safety of different doses of consensus interferon plus ribavirin in the initial treatment of chronic hepatitis C. **Methods:** One hundred and one genotype 2/3 patients were randomized to receive 9 mcg (group A, n=48) or 18 mcg (group B, n=53) of consensus interferon thrice weekly plus ribavirin (1000/1200 mg/daily) for 24 weeks and 92 genotype 1 patients to receive 9 mcg (group C, n=47) or 18 mcg (group D, n=45) of consensus interferon plus ribavirin for 48 weeks. Results: In an intention-to-treat analysis, the sustained virologic response at 24-week follow-up was 69% and 66% for group A and B (P=0.77) and 40% and 36% for group C and D (P=0.63). The overall sustained response was 67% and 38% in patients with genotype 2/3 and 1, respectively. Among genotype 1 patients the sustained virologic response was 39% and 41% for high or low baseline viremia levels. **Conclusions:** Higher consensus interferon dose does not increase sustained virologic response. Naive genotype 1 patients may achieve significant response rate of approximately 40% if treated with 9 mcg of consensus interferon plus ribavirin for 48 weeks.

Distribution of hepatitis B viral genotypes and mutations in the core promoter and precore regions in acute forms of liver disease in patients from Chiba, Japan

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Background: Although it has been reported that different hepatitis B virus (HBV) genotypes induce different clinical characteristics in patients with chronic liver diseases (CLD), there have been few reports that have detailed the distribution of HBV genotypes in acute forms of liver disease. **Methods**: HBV genotypes were determined in 61 patients who had acute forms of liver disease (45 had acute self limited hepatitis (AH) and 16 had fulminant hepatitis (FH)) and in 531 patients with CLD, including 19 patients with severe acute exacerbation of CLD. We also analysed the enhancer II, core promoter, and precore region sequences for the presence of mutations. **Results**: Expression of genotype B in patients with acute forms of liver disease was significantly greater than in those with CLD (39.3% v 11.7%, respectively; $p<0.001$).

Furthermore, expression of genotype B was significantly greater in patients with FH than in those with AH (62.5% v 31.1%, respectively; p=0.027). The precore mutation A1896 and the core promoter mutation at nt 1753 and 1754 were found more frequently in FH than in AH, and genotype B was predominant in FH regardless of the presence of these mutations. **Conclusions**: HBV genotype B was found more frequently in patients with acute forms of liver disease than in patients with CLD, and more frequently in patients with FH than in those with AH. These results suggest that this HBV genotype may induce more severe liver damage than other viral genotypes, at least in patients from Chiba, Japan.

Comprehensive Analysis of Class I and Class II HLA Antigens and Chronic Hepatitis B Virus Infection

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Following an acute hepatitis B virus (HBV) infection, clearance or persistence is determined in part by the vigor and breadth of the host immune response. Since the human leukocyte antigen system (HLA) is an integral component of the immune response, we hypothesized that the highly polymorphic HLA genes are key determinants of viral clearance. HLA class I and II genes were molecularly typed in 194 Caucasian individuals with viral persistence and 342 matched controls who had cleared the virus. A single class I allele, A*0301 (odds ratio [OR], 0.47; 95% confidence interval [CI], 0.30 to 0.72; P = 0.0005) was associated with viral clearance. The class II allele DRB1*1302 was also associated with clearance (OR, 0.42; 95% CI, 0.19 to 0.93; P = 0.03), but its significance decreased in a multivariate model that included other alleles associated with disease outcome as covariates. B*08 was associated with viral persistence both independently (OR, 1.59; 95% CI, 1.04 to 2.43; P = 0.03) and as part of the conserved Caucasian haplotype A*01-B*08-DRB1*03. The B*44-Cw*1601 (OR, 2.23; 95% CI, 1.13 to 4.42; P = 0.02) and B*44-Cw*0501 (OR, 1.99; 95% CI, 1.22 to 3.24; P = 0.006) haplotypes were also associated with viral persistence. Interestingly, both the B*08 haplotype and DR7, which forms a haplotype with B*44-Cw*1601, have been associated with nonresponse to the HBV vaccine. The associations with class I alleles are consistent with a previously implicated role for CD8-mediated cytolytic-T-cell response in determining the outcome of an acute HBV infection.